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(54) **ANTIBODY SPECIFICALLY BINDING TO ERBB3 AND USE THEREOF**

(57) An antibody that specifically binds to ErbB3 or an antigen-binding fragment thereof, and use thereof, are provided. The antibody that specifically binds to ErbB3 or an antigen-binding fragment thereof may be effectively used to prevent or treat a disease related to activation or overexpression of ErbB3 protein.

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Description

Technical Field

[0001] One or more example embodiments relate to an antibody specifically binding to a receptor tyrosine kinase ErbB3 protein or an antigen-binding fragment of the antibody, a method of preparing the same, and use thereof.

Background Art

[0002] The epidermal growth factor receptor (EGFR or ErbB) family of receptor tyrosine kinases includes ErbB1 (known also as epidermal growth factor receptor (EGFR)), ErbB2 (known also as human epidermal growth factor receptor 2 (HER2)), ErbB3 (known also as HER3), and ErbB4 (known also as HER4). The receptor tyrosine kinases of the ErbB family may form a homodimer or heterodimer by combination with a ligand and may activate the signal transduction pathway of mitogen-activated protein kinase kinase (MAP2K, MEK, or MAPKK)/ mitogen-activated protein kinase (MAPK), or the signal transduction pathway of phosphoinositide 3-kinase (PI3K)/ protein kinase B (PKB or Akt). The ErbB family of proteins is reported to be related to the occurrence, progress, or prognosis of cancer.

[0003] Erbitux® (Cetuximab) or Tarceva® (Erlotinib) as ErbB1 inhibitors and Herceptin® (Trastuzumab) or Tyverb® (Lapatinib) as ErbB2 inhibitors, are commercially available anti-cancer drugs. However, a large number of patients are unresponsive to these anti-cancer drugs, and these anti-cancer drugs are accompanied with development of resistance. A specific inhibitor antibody to ErbB3 or ErbB4 has not yet been made commercially available.

[0004] Therefore, there is a need for the development of new anti-cancer drugs that may cope with the genetic diversity of cancer and overcome resistance to anti-cancer drugs.

Disclosure of Invention

Technical Problem

[0005] One or more example embodiments include an antibody specifically binding to ErbB3, or an antigen-binding fragment thereof.

[0006] One or more example embodiments include a pharmaceutical composition for prevention or treatment of a disease related to the activation or overexpression of ErbB3 protein.

[0007] One or more example embodiments include a method of prevention or treatment of a disease related to the activation or overexpression of ErbB3 protein in an individual.

Solution to Problem

[0008] This application claims the benefit of Korean Patent Application No. 10-2015-0173281, filed on December 7, 2015, in the Korean Intellectual Property Office.

[0009] Reference will now be made in detail to example embodiments, which are illustrated in the accompanying drawings, wherein like reference numerals refer to like elements throughout. In this regard, the present example embodiments may have different forms and should not be construed as being limited to the descriptions set forth herein. Accordingly, the example embodiments are merely described below, by referring to the figures, to explain aspects of the present description. As used herein, the term "and/or" includes any and all combinations of one or more of the associated listed items. Expressions such as "at least one of," when preceding a list of elements, modify the entire list of elements and do not modify the individual elements of the list.

[0010] According to an aspect of the present disclosure, an antibody specifically binding to ErbB3 or an antigen-binding fragment of the antibody includes:

a heavy chain variable region including at least one amino acid sequence selected from the group consisting of SEQ ID NOs: 61 to 85, and 102;
a light chain variable region including at least one amino acid sequence selected from the group consisting of SEQ ID NOs: 86 to 101, and 103; or
the heavy chain variable region and the light chain variable region.

[0011] There are five types of heavy chains denoted by γ, δ, α, μ, and ε. The type of heavy chain defines the class of antibody. The heavy chain types α and γ each chain consists of approximately 450 amino acids, whereas μ and ε each chain consists of approximately 550 amino acids. Each heavy chain has two regions, i.e., the variable region and the constant region.

[0012] There are two types of light chains denoted by λ and κ. Each light chain consists of approximately 211 to 217 amino acids. Each human antibody contains only one type of light chain. Each light chain contains two successive domains including one constant region and one variable region.

[0013] The variable region refers to a region of the antibody which binds to an antigen.

[0014] The heavy chain variable region may include: a complementarity-determining region-H1 (CDR-H1) including an amino acid sequence selected from the group consisting of SEQ ID. NOs: 61 to 68; a CDR-H2 including an amino acid sequence selected from SEQ ID NOs: 69 to 77, and 102; and a CDR-H3 including an amino acid sequence selected from SEQ ID NOs: 78 to 85. For example, the heavy chain variable region may include an amino acid sequence selected from the group consisting of SEQ ID NOs: 1 to 30. The term "complementarity-determining region (CDR)" refers to a site of the variable region of an antibody that imparts binding specificity of the antibody or antigen-binding fragment thereof to an antigen.

[0015] The light chain variable region may include: a CDR-L1 including an amino acid sequence selected from the group consisting of SEQ ID NOs: 86, 87, and 103; a CDR-L2 including an amino acid sequence selected from the group consisting of SEQ ID NOs: 88 to 93; and a CDR-L3 including an amino acid sequence selected from the group consisting of SEQ ID NOs: 94 to 101. For example, the light chain variable region may include an amino acid sequence selected from the group consisting of SEQ ID NOs: 31 to 60.

[0016] The antibody or the antigen-binding fragment thereof may include a heavy chain variable region selected from the group consisting of heavy chain variable regions CDR-H1, CDR-H2, and CDR-H3, which represent amino acid sequences listed in Table 5.

[Table 5]

No.	CDR-H1	CDR-H2	CDR-H3
1	DYDMS (SEQ ID NO: 61)	SIYPDSGSTYYADSVQG (SEQ ID NO: 69)	DLHMGPEGPFDY (SEQ ID NO: 78)
2	DYDMS (SEQ ID NO: 61)	TIDLDSGSIYYADSVQG (SEQ ID NO: 70)	DLHMGPEGPFDY (SEQ ID NO: 78)
3	DYDMS (SEQ ID NO: 61)	SIYPDSGSTDYADSVQG (SEQ ID NO: 71)	DLHMGPEGPFDY (SEQ ID NO: 78)
4	DYDMS (SEQ ID NO: 61)	SIEPDFGSSYYADSVRG (SEQ ID NO: 72)	DLHMGPEGPFDY (SEQ ID NO: 78)
5	DYDMS (SEQ ID NO: 61)	IIEPDSGSIYYADSVQG (SEQ ID NO: 73)	DLHMGPEGPFDY (SEQ ID NO: 78)
6	DYDMS (SEQ ID NO: 61)	SIYPDSGSTDYADSVQG (SEQ ID NO: 71)	DRHMWPEGPFDY (SEQ ID NO: 79)
7	DYDMS (SEQ ID NO: 61)	SIYPDSGSTYYADSVQG (SEQ ID NO: 69)	DRHMWPEGPFDY (SEQ ID NO: 79)
8	DYDMS (SEQ ID NO: 61)	SIYPDSGSTYYADSVQG (SEQ ID NO: 69)	DRHMWPEGPFDY (SEQ ID NO: 79)
9	DYDMS (SEQ ID NO: 61)	SIYPDSGSTYYADSVQG (SEQ ID NO: 69)	DRHMWPEGPFDY (SEQ ID NO: 79)
10	DYDMS (SEQ ID NO: 61)	TIDLDSGSIYYADSVQG (SEQ ID NO: 70)	DLHMGPEGPFDY (SEQ ID NO: 78)
11	DYDMS (SEQ ID NO: 61)	TIDLDSGSIYYADSVQG (SEQ ID NO: 70)	DLHMGPEGPFDY (SEQ ID NO: 78)
12	DYDMS (SEQ ID NO: 61)	SIEPDSGSTDYADSVQG (SEQ ID NO: 74)	DRHMWPEGPFDY (SEQ ID NO: 79)

(continued)

No.	CDR-H1	CDR-H2	CDR-H3
13	DYDMS (SEQ ID NO: 61)	TIEPDSGSTYYADSVQS (SEQ ID NO: 75)	DLHMGPEGPFDY (SEQ ID NO: 78)
14	DYDMS (SEQ ID NO: 61)	SIYPDSGSTYYADSVQG (SEQ ID NO: 69)	DLHMGPEGPFDY (SEQ ID NO: 78)
15	DYDMS (SEQ ID NO: 61)	SIYPDSGSTDYADSVQG (SEQ ID NO: 71)	DLHMWPEGPFDY (SEQ ID NO: 80)
16	DYDMS (SEQ ID NO: 61)	TIEPDYGSTLYADSVQG (SEQ ID NO: 102)	DLHMGPEGPFDY (SEQ ID NO: 78)
17	DYDMS (SEQ ID NO: 61)	GISYDGGNTYYADSVKG (SEQ ID NO: 76)	DPSWCLQDLCYYADGMDV (SEQ ID NO: 81)
18	WYDMT (SEQ ID NO: 62)	GISYDGGNTYYADSVKG (SEQ ID NO: 76)	DPSWCLQDLCYYADGMDV (SEQ ID NO: 81)
19	WYDLA (SEQ ID NO: 63)	GISYDGGNTYYADSVKG (SEQ ID NO: 76)	DPSWCLQDLCYYADGMDV (SEQ ID NO: 81)
20	WYDMS (SEQ ID NO: 64)	GISYDGGNTYYADSVKG (SEQ ID NO: 76)	DPSWCLQDLCYYADGMDV (SEQ ID NO: 81)
21	WYDIA (SEQ ID NO: 65)	GISYDGGNTYYADSVKG (SEQ ID NO: 76)	DPSWCLQDLCYYADGMDV (SEQ ID NO: 81)
22	WYDLS (SEQ ID NO: 66)	GISYDGGNTYYADSVKG (SEQ ID NO: 76)	DPSWCLQDLCYYADGMDV (SEQ ID NO: 81)
23	DYDMS (SEQ ID NO: 61)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFVSDSTFDY (SEQ ID NO: 82)
24	DYDMS (SEQ ID NO: 61)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFMSDSTFDY (SEQ ID NO: 83)
25	DYDMS (SEQ ID NO: 61)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFASDSTFDY (SEQ ID NO: 84)
26	HYDMS (SEQ ID NO: 67)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFASDSTFDY (SEQ ID NO: 84)
27	YYDMS (SEQ ID NO: 68)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFASDSTFDY (SEQ ID NO: 84)
28	DYDMS (SEQ ID NO: 61)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFESDSTFDY (SEQ ID NO: 85)
29	HYDMS (SEQ ID NO: 67)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFESDSTFDY (SEQ ID NO: 85)
30	YYDMS (SEQ ID: 68)	AIYYDSGSIYYADSAKG (SEQ ID: 77)	DRLFESDSTFDY (SEQ ID: 85)

[0017] For example, the antibody or the antigen-binding fragment thereof may include a heavy chain variable region that includes a CDR-H1 including an amino acid sequence of SEQ ID NO: 61, a CDR-H2 including an amino acid sequence of SEQ ID NO: 69, and a CDR-H3 including an amino acid sequence of SEQ ID NO: 78.

[0018] The antibody or the antigen-binding fragment thereof may include a light chain variable region selected from the group consisting of light chain variable regions CDR-L1, CDR-L2, and CDR-L3, which include amino acid sequences

listed in Table 6.

[Table 6]

No.	CDR-L1	CDR-L2	CDR-L3
31	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
32	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	QGWDTSLSGHV (SEQ ID NO: 95)
33	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
34	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
35	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
36	SGSSSN IGSNSGS (SEQ ID NO: 87)	ADNWRPS (SEQ ID NO: 89)	AAWDSSLSGYV (SEQ ID NO: 94)
37	SGSSSN IGSNSGS (SEQ ID NO: 87)	ADNHRPS (SEQ ID NO: 90)	AAWDSSLSGYV (SEQ ID NO: 94)
38	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
39	SGSSSN IGSNSGS (SEQ ID NO: 87)	ADNWRPS (SEQ ID NO: 89)	AAWDSSLSGYV (SEQ ID NO: 94)
40	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	VGWDSSLYGHV (SEQ ID NO: 96)
41	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	HAWDSSLWGDV (SEQ ID NO: 97)
42	SGSSSN IGSNSGS (SEQ ID NO: 87)	ADNWRPS (SEQ ID NO: 89)	AAWDSSLSGYV (SEQ ID NO: 94)
43	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
44	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	HAWDSSLYVDV (SEQ ID NO: 98)
45	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADNFRPS (SEQ ID NO: 91)	AAWDSSLSGYV (SEQ ID NO: 94)
46	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	HAWDSSLSGDF (SEQ ID NO: 99)
47	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
48	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
49	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
50	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
51	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
52	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
53	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
54	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
55	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
56	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
57	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
58	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
59	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
60	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)

[0019] For example, the antibody or the antigen-binding fragment thereof may include a light chain variable region that includes a CDR-L1 including an amino acid sequence of SEQ ID NO: 86, a CDR-L2 including an amino acid sequence of SEQ ID NO: 88, and a CDR-L3 including an amino acid sequence of SEQ ID NO: 94.

[0020] The ErbB3 may be an ErbB3 polypeptide or a fragment thereof. The ErbB3 polypeptide may be a human amino acid sequence with GenBank Accession No. NP_001005915, or a mouse amino acid sequence with GenBank Accession No. NP_034283. The fragment of the ErbB3 polypeptide may be a polypeptide including a partial amino acid sequence of the ErbB3 polypeptide. The ErbB3 is a receptor tyrosine kinase of the epidermal growth factor receptor (EGFR or ErbB) family, and is known also as HER3.

[0021] The antibody or the antigen-binding fragment thereof that specifically binds to ErbB3 may have affinity to an ErbB3 polypeptide or a fragment thereof.

[0022] The antibody or the antigen-binding fragment thereof may inhibit binding of ErbB3 protein with a material that specifically binds to ErbB3 protein, dimerization of ErbB1 protein and ErbB3 protein, dimerization of ErbB2 protein and ErbB3 protein, phosphorylation of ErbB3 or Akt, or a combination thereof. The material specifically binding to ErbB3 protein may be heregulin (HRG).

[0023] The term "antibody" is interchangeably used with "immunoglobulin (Ig)." The whole antibody has a structure including two full-length light chains and two full-length heavy chains, which are connected by disulfide (SS) bonds. The antibody may be, for example, IgA, IgD, IgE, IgG, or IgM. The antibody may be a monoclonal antibody or a polyclonal antibody. The antibody may be an animal-derived antibody, a mouse-human chimeric antibody, a humanized antibody, or a human antibody.

[0024] The term "antigen-binding fragment" refers to a fragment of the whole immunoglobulin structure, which may be a part of a polypeptide including an antigen-binding site. For example, the antigen-binding fragment may be scFv, $(scFv)_2$, Fv, Fab, Fab', Fv $F(ab')_2$, or a combination thereof.

[0025] The antibody or the antigen-binding fragment thereof may be modified. For example, the antibody or the antigen-binding fragment thereof may be modified by conjugation or binding, glycosylation, tag attachment, or a combination thereof. The antibody may be conjugated with other drugs such as anti-cancer drug. For example, the antibody or the antigen-binding fragment thereof may be conjugated with horseradish peroxidase (HRP), alkaline phosphatase, hapten, biotin, streptavidin, a fluorescent material, a radioactive material, quantum dots, polyethylene glycol (PEG), a histidine tag, or a combination thereof. The fluorescent material may be Alexa Fluor®532, Alexa Fluor®546, Alexa Fluor®568, Alexa Fluor®680, Alexa Fluor®750, Alexa Fluor®790, or Alexa Fluor™ 350.

[0026] According to another aspect of the present disclosure, a pharmaceutical composition for prevention or treatment of a disease related to activation or overexpression of ErbB3 protein includes the antibody or the antigen-binding fragment thereof according to any of the above-described example embodiments.

[0027] The antibody, antigen-binding fragment, and ErbB3 protein are the same as described above.

[0028] The disease related to the activation or overexpression of ErbB3 protein may be cancer. The cancer may be a solid cancer or a non-solid cancer. Solid cancers refer to the incidence of cancerous tumors in solid organs such as the liver, lung, breast, or skin, whereas non-solid cancers refer to cancers affecting the blood, and so are called blood cancer. For example, the cancer may be selected from the group consisting of breast cancer, skin cancer, head and neck cancer, pancreatic cancer, lung cancer, colon cancer, colorectal cancer, gastric cancer, ovarian cancer, prostate cancer, bladder cancer, uterine cancer, liver cancer, kidney cancer, clear cell sarcoma, melanoma, cerebrospinal tumors, brain cancer, thymoma, mesothelioma, esophageal cancer, biliary tract cancer, testicular cancer, germinal cancer, thyroid cancer, parathyroid cancer, cervical cancer, endometrial cancer, lymphoma, myelodysplastic syndromes (MDS), myelofibrosis, acute leukemia, chronic leukemia, multiple myeloma, Hodgkin's disease, endocrine cancer, and sarcoma.

[0029] The term "prevention" refers to any act that suppresses or delays the onset of a disease related to the activation or overexpression of ErbB3 protein by administration of the pharmaceutical composition. The term "treatment" refers to any act that alleviates symptoms of a disease related to the activation or overexpression of ErbB3 protein by administration of the pharmaceutical composition.

[0030] The pharmaceutical composition may include a pharmaceutically acceptable carrier. The carrier may be construed as meaning an excipient, a diluent, or an adjuvant. For example, the carrier may be selected from the group consisting of lactose, dextrose, sucrose, sorbitol, mannitol, xylitol, erythritol, maltitol, starch, acacia rubber, alginate, gelatin, calcium phosphate, calcium silicate, cellulose, methyl cellulose, polyvinylpyrrolidone, water, physiological saline, a buffer such as phosphate-buffered saline (PBS), methyl hydroxybenzoate, propyl hydroxybenzoate, talc, magnesium stearate, glycine, histidine, serine, polysorbate, and mineral oil. The pharmaceutical composition may include a filler, an anti-coagulant, a lubricant, a wetting agent, a flavoring agent, an emulsifier, a preservative, or a combination thereof.

[0031] The pharmaceutical composition may be formulated in any form using any common method in the art. For example, the pharmaceutical composition may be formulated in oral dosage form (for example, powders, tablets, capsules, syrups, pills, or granules), or parenteral dosage form (for example, injection). The pharmaceutical composition may be prepared in formulation for systemic delivery, or in a formulation for local delivery.

[0032] The pharmaceutical composition may further include an anti-cancer drug. The anti-cancer drug may be Cetuximab, Panitumumab, Erlotinib, Gefitinib, Trastuzumab, T-DM1, Pertuzumab, Lapatinib, Paclitaxel, Tamoxifen, Cisplatin, anti-CTLA-4 antibody, anti-PD-1 antibody, anti-PD-L1 antibody, 5-fluorouracil (5FU), Gemcitabine, or a combination thereof. The pharmaceutical composition may include a single composition or separate compositions. For example, the antibody or the antigen-binding fragment thereof of the pharmaceutical composition may be a composition in parenteral dosage form, and the anti-cancer drug may be a composition in oral dosage form.

[0033] The pharmaceutical composition may include an effective amount of the antibody or the antigen-binding fragment thereof, an anti-cancer drug, or a combination thereof. The term "effective amount" used herein refers to an amount sufficient to prevent or treat a disease related to activation or overexpression of ErbB3 protein when administered to an

individual who needs such prevention or treatment. The effective amount may be appropriately selected depending on a selected cell or individual by one of ordinary skill in the art. For example, the effective amount may be determined depending on disease severity, a patient's age, body weight, health conditions, gender, a patient's drug sensitivity, administration duration, administration route, excretion rate, treatment duration, and other factors, including use of a drug in combination with or at the same time as the pharmaceutical composition, and other factors known in the medical field. The effective amount may be about 0.5 μg to about 2 g, about 1 μg to about 1 g, about 10 μg to about 500 mg, about 100 μg to about 100 mg, or about 1 mg to about 50 mg of the pharmaceutical composition.

[0034] A dose of the pharmaceutical composition may be, for example, about 0.001 mg/kg to about 100 mg/kg, about 0.01 mg/kg to about 10 mg/kg, or about 0.1 mg/kg to about 1 mg/kg when administered to an adult. The number of administrations may be, for example, once or multiple times a day, once a week, once in two weeks, once in three weeks, once in four weeks, or once a year.

[0035] According to another aspect of the present disclosure, a method of prevention or treatment of a disease related to activation or overexpression of ErbB3 protein in an individual includes administering the antibody or an antigen-binding fragment thereof according to any of the above-described example embodiments to the individual.

[0036] The antibody, antigen-binding fragment, ErbB3 protein, disease related to the activation or overexpression of ErbB3 protein, prevention, or treatment may be the same as described above.

[0037] The individual may be a mammal, for example, a human, cow, horse, pig, dog, sheep, goat, or cat. The individual may be an individual who suffers from a disease related to the activation or overexpression of ErbB3 protein or who is susceptible to the disease, which may be cancer.

[0038] The method may further include administering an anti-cancer drug to the individual. The anti-cancer drug may be administered at the same time with, separately from, or sequentially with the antibody or an antigen-binding fragment thereof according to any of the above-described example embodiments.

[0039] For example, the antibody or the antigen-binding fragment thereof, an anti-cancer drug, or a combination thereof may be directly administered to the individual by any method, for example, by oral, intravenous, intramuscular, transdermal, mucosal, intranasal, intratracheal, or subcutaneous administration. The antibody or the antigen-binding fragment thereof, an anti-cancer drug, or a combination thereof may be administered systemically or locally. The antibody or the antigen-binding fragment thereof, an anti-cancer drug, or a combination thereof may be administered alone or together with a pharmaceutically active compound.

[0040] A dose of the antibody or the antigen-binding fragment thereof, an anti-cancer drug, or a combination thereof may vary depending on a patient's condition, body weight, disease severity, drug formulation, administration route, and administration duration, and may be appropriately selected by one of ordinary skill in the art. For example, a dose of the antibody or the antigen-binding fragment thereof, an anti-cancer drug, or a combination thereof may be about 0.001 mg/kg to about 100 mg/kg, about 0.01 mg/kg to about 10 mg/kg, or about 0.1 mg/kg to about 1 mg/kg when administered to an adult. The number of administrations may be, for example, once or multiple times a day, once a week, once in two weeks, once in three weeks, once in four weeks, or once a year.

[0041] According to another aspect of the present disclosure, a method of prevention or treatment of cancer drug resistance in an individual includes administering the antibody or the antigen-binding fragment of any one of claims 1 to 10 to the individual.

Brief Description of Drawings

[0042] These and/or other aspects will become apparent and more readily appreciated from the following description of the example embodiments, taken in conjunction with the accompanying drawings in which:

FIGS. 1a and 1b illustrate amino acid sequences and complementarity-determining regions (CDRs) in variable regions of heavy chains (FIG. 1a) and light chains (FIG. 1b) of lead antibodies and modified antibodies thereof;

FIG. 2 is a graph showing the binding affinity (%) of ErbB3 protein and HRG in the presence of anti-ErbB3 antibodies;

FIG. 3 is a graph showing the binding affinity (%) of ErbB2 protein and ErbB3 protein in the presence of anti-ErbB3 antibodies;

FIGS. 4a and 4b are graphs showing phosphorylation ratios (%) of ErbB3 and Akt, respectively, in the presence of anti-ErbB3 antibodies;

FIG. 5 is a graph of relative proliferation (%) of BxPC3 pancreatic cancer cells in the presence of anti-ErbB3 antibodies;

FIG. 6 is a graph of tumor volume (mm^3) in a BT474 breast cancer xenograft model after administration of anti-ErbB3 antibodies;

FIG. 7 is a graph of tumor volume (mm^3) in a MDA-MB-468 breast cancer xenograft model after administration of anti-ErbB3 antibodies;

FIG. 8 is a graph of tumor volume (mm^3) in an A431 skin cancer xenograft model after administration of anti-ErbB3 antibodies;

FIG. 9 is a graph of tumor volume (mm^3) in a FaDu head and neck cancer xenograft model after administration of anti-ErbB3 antibodies or combined administration of anti-ErbB3 antibodies and Cetuximab;
FIG. 10 is a graph of the activity of caspase 3/7 (in relative luminance units (RLU)) in breast cancer cells after combined administration of paclitaxel, HRG, and anti-ErbB3 antibody;
FIG. 11 is a graph of cancer cell proliferation rate (%) in colorectal cancer cells after combined administration of Cetuximab, HRG, and anti-ErbB3 antibody; and
FIG. 12 is a graph of tumor volume in an Cetuximab-resistant xenograft model after combined administration of Cetuximab and anti-ErbB3 antibody.

Mode for the Invention

[0043] Hereinafter, one or more embodiments of the present disclosure will now be described in detail with reference to the following examples. However, these examples are only for illustrative purposes and are not intended to limit the scope of the one or more embodiments of the present disclosure.

Example 1. Preparation of anti-ErbB3 antibody

1. Screening of lead antibody

[0044] To obtain human anti-ErbB3 antibodies, the human synthetic scFv-phage display library (provided by H.B. SHIM of Ewha Womans University, Korea) was screened against ErbB3 protein (R&D systems) to obtain phage displaying scFv fragments that bind to ErbB3.

[0045] Nucleic acid sequences encoding the scFV fragments of the obtained phage were analyzed, and amino acid sequences of the VH and VL domains of the scFv fragments that bind to ErbB3 were identified by amino acid sequence analysis. After the sequences of the scFv fragments that bind to ErbB3 were obtained, the VH and VL domains were reconstructed using a Selexis 085 vector (Selexis) encoding IgG1, to thereby assemble the whole antibody gene. The reconstructed expression vectors encoding IgG1 were transformed and expressed at a small scale in Chinese hamster ovary (CHO) cell lines. The expressed anti-ErbB3 antibodies were subjected to measurement of binding affinity to ErbB3 and cellular-based analysis, to thereby screen anti-ErbB3 lead antibodies 442P, 472P, and 451P that inhibit heregulin (HRG)-dependent ErbB3 signal transduction.

2. Screening of modified antibodies from lead antibodies

[0046] Fab-phage display libraries were constructed by introducing mutations into six CDR sites of the screened anti-ErbB3 lead antibodies 442P, 472P, and 451P of Example 1.1 by random mutagenesis. The Fab-phage display libraries were amplified by polymerase chain reaction (PCR) with primers (by Integrated DNA Technologies, Inc.), which were made to order, and Phusion polymerase (New England Biolabs).

[0047] The constructed Fab-phage display libraries were screened against the recombinant human ErbB3 protein (R&D systems) to screen for antibodies with improved binding affinity to the recombinant human ErbB3, as compared with the lead antibodies. The screened antibodies were reconstructed to IgG as described in Example 1.1 and transformed and expressed at a small scale in CHO cell lines.

[0048] The binding affinity of the anti-ErbB3 antibodies was measured using an Octet® QK384 system (Pall Life Sciences). The antibodies with improved binding affinity compared to the lead antibodies were screened based on the results and subjected to cellular-based analysis to verify efficacy. Amino acid sequences of the variable regions of the anti-ErbB3 lead antibodies and the modified antibodies were analyzed, and complementarity-determining regions (CDRs) were determined according to the Kabat definition. The amino acid sequences (SEQ ID NOs: 1 to 60) in the various regions of heavy chains and light chains of the screened antibodies are presented in FIGS. 1a and 1b, and the amino acid sequences in the CDRs of the heavy chains and light chains are shown in Table 1 and 2, respectively.

[Table 1]

Antibod y	CDR-H1	CDR-H2	CDR-H3
442P	DYDMS (SEQ ID NO: 61)	SIYPDSGSTYYADSVQG (SEQ ID NO: 69)	DLHMGPEGPFDY (SEQ ID NO: 78)
442S1	DYDMS (SEQ ID NO: 61)	TIDLDSGSIYYADSVQG (SEQ ID NO: 70)	DLHMGPEGPFDY (SEQ ID NO: 78)

(continued)

Antibod y	CDR-H1	CDR-H2	CDR-H3
442S2	DYDMS (SEQ ID NO: 61)	SIYPDSGSTDYADSVQG (SEQ ID NO: 71)	DLHMGPEGPFDY (SEQ ID NO: 78)
442S4	DYDMS (SEQ ID NO: 61)	SIEPDFGSSYYADSVRG (SEQ ID NO: 72)	DLHMGPEGPFDY (SEQ ID NO: 78)
442S5	DYDMS (SEQ ID NO: 61)	IIEPDSGSIYYADSVQG (SEQ ID NO: 73)	DLHMGPEGPFDY (SEQ ID NO: 78)
442S6	DYDMS (SEQ ID NO: 61)	SIYPDSGSTDYADSVQG (SEQ ID NO: 71)	DRHMWPEGPFDY (SEQ ID NO: 79)
442S9	DYDMS (SEQ ID NO: 61)	SIYPDSGSTYYADSVQG (SEQ ID NO: 69)	DRHMWPEGPFDY (SEQ ID NO: 79)
442S10	DYDMS (SEQ ID NO: 61)	SIYPDSGSTYYADSVQG (SEQ ID NO: 69)	DRHMWPEGPFDY (SEQ ID NO: 79)
442M3	DYDMS (SEQ ID NO:	SIYPDSGSTYYADSVQG	DRHMWPEGPFDY
	61)	(SEQ ID NO: 69)	(SEQ ID NO: 79)
442M4	DYDMS (SEQ ID NO: 61)	TIDLDSGSIYYADSVQG (SEQ ID NO: 70)	DLHMGPEGPFDY (SEQ ID NO: 78)
442M5	DYDMS (SEQ ID NO: 61)	TIDLDSGSIYYADSVQG (SEQ ID NO: 70)	DLHMGPEGPFDY (SEQ ID NO: 78)
442M6	DYDMS (SEQ ID NO: 61)	SIEPDSGSTDYADSVQG (SEQ ID NO: 74)	DRHMWPEGPFDY (SEQ ID NO: 79)
442M7	DYDMS (SEQ ID NO: 61)	TIEPDSGSTYYADSVQS (SEQ ID NO: 75)	DLHMGPEGPFDY (SEQ ID NO: 78)
442M8	DYDMS (SEQ ID NO: 61)	SIYPDSGSTYYADSVQG (SEQ ID NO: 69)	DLHMGPEGPFDY (SEQ ID NO: 78)
442M10	DYDMS (SEQ ID NO: 61)	SIYPDSGSTDYADSVQG (SEQ ID NO: 71)	DLHMWPEGPFDY (SEQ ID NO: 80)
442M11	DYDMS (SEQ ID NO: 61)	TIEPDYGSTLYADSVQG (SEQ ID NO: 102)	DLHMGPEGPFDY (SEQ ID NO: 78)
472P	DYDMS (SEQ ID NO: 61)	GISYDGGNTYYADSVKG (SEQ ID NO: 76)	DPSWCLQDLCYYADG MDV (SEQ ID NO: 81)
472S1	WYDMT (SEQ ID NO: 62)	GISYDGGNTYYADSVKG (SEQ ID NO: 76)	DPSWCLQDLCYYADG MDV (SEQ ID NO: 81)
472S2	WYDLA (SEQ ID NO: 63)	GISYDGGNTYYADSVKG (SEQ ID NO: 76)	DPSWCLQDLCYYADG MDV (SEQ ID NO: 81)
472S3	WYDMS (SEQ ID NO: 64)	GISYDGGNTYYADSVKG (SEQ ID NO: 76)	DPSWCLQDLCYYADG MDV (SEQ ID NO: 81)
472S4	WYDIA (SEQ ID NO: 65)	GISYDGGNTYYADSVKG (SEQ ID NO: 76)	DPSWCLQDLCYYADG MDV (SEQ ID NO: 81)

(continued)

Antibod y	CDR-H1	CDR-H2	CDR-H3
472M1	WYDLS (SEQ ID NO: 66)	GISYDGGNTYYADSVKG (SEQ ID NO: 76)	DPSWCLQDLCYYADG MDV (SEQ ID NO: 81)
451P	DYDMS (SEQ ID NO: 61)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFVSDSTFDY (SEQ ID NO: 82)
451M1	DYDMS (SEQ ID NO:	AIYYDSGSIYYADSAKG	DRLFMSDSTFDY (SEQ
	61)	(SEQ ID NO: 77)	ID NO: 83)
451M2	DYDMS (SEQ ID NO: 61)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFASDSTFDY (SEQ ID NO: 84)
451M3	HYDMS (SEQ ID NO: 67)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFASDSTFDY (SEQ ID NO: 84)
451M4	YYDMS (SEQ ID NO: 68)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFASDSTFDY (SEQ ID NO: 84)
451M5	DYDMS (SEQ ID NO: 61)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFESDSTFDY (SEQ ID NO: 85)
451M6	HYDMS (SEQ ID NO: 67)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFESDSTFDY (SEQ ID NO: 85)
451M7	YYDMS (SEQ ID NO: 68)	AIYYDSGSIYYADSAKG (SEQ ID NO: 77)	DRLFESDSTFDY (SEQ ID NO: 85)

[Table 2]

Antibod y	CDR-L1	CDR-L2	CDR-L3
442P	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
442S1	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	QGWDTSLSGHV (SEQ ID NO: 95)
442S2	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
442S4	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
442S5	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
442S6	SGSSSN IGSNSGS (SEQ ID NO: 87)	ADNWRPS (SEQ ID NO: 89)	AAWDSSLSGYV (SEQ ID NO: 94)
442S9	SGSSSN IGSNSGS (SEQ ID NO: 87)	ADNHRPS (SEQ ID NO: 90)	AAWDSSLSGYV (SEQ ID NO: 94)
442S10	SGSSSNIGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
442M3	SGSSSN IGSNSGS (SEQ ID NO: 87)	ADNWRPS (SEQ ID NO: 89)	AAWDSSLSGYV (SEQ ID NO: 94)
442M4	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	VGWDSSLYGHV (SEQ ID NO: 96)

(continued)

Antibody	CDR-L1	CDR-L2	CDR-L3
442M5	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	HAWDSSLWGDV (SEQ ID NO: 97)
442M6	SGSSSN IGSNSGS (SEQ ID NO: 87)	ADNWRPS (SEQ ID NO: 89)	AAWDSSLSGYV (SEQ ID NO: 94)
442M7	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	AAWDSSLSGYV (SEQ ID NO: 94)
442M8	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	HAWDSSLYVDV (SEQ ID NO: 98)
442M10	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADNFRPS (SEQ ID NO: 91)	AAWDSSLSGYV (SEQ ID NO: 94)
442M11	SGSSSN IGSNSVS (SEQ ID NO: 86)	SDNHRPS (SEQ ID NO: 88)	HAWDSSLSGDF (SEQ ID NO: 99)
472P	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
472S1	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
472S2	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
472S3	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
472S4	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
472M1	SGSSSN IGSNSVS (SEQ ID NO: 86)	ADSNRPS (SEQ ID NO: 92)	GSWDYSLSGYV (SEQ ID NO: 100)
451P	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
451M1	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
451M2	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
451M3	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
451M4	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
451M5	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
451M6	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)
451M7	SGSPSNIGNNSVT (SEQ ID NO: 103)	YDSHRPS (SEQ ID NO: 93)	GSWDASLNGYV (SEQ ID NO: 101)

Example 2. *In-vitro* effect of anti-ErbB3 antibody

1. Binding affinity of anti-ErbB3 antibody to human ErbB3 protein

[0049] Binding affinities of the screened antibodies (Example 1.2) to ErbB3 protein (antigen) were measured.

[0050] In particular, the binding affinities of the anti-ErbB3 antibodies to the recombinant human ErbB3 protein (R&D systems) and the antigen-antibody interactive dynamics were measured using an Octet® QK384 system (Pall Life Sciences). After activation of carboxyl groups in 20 mM of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) and 40 mM of N-hydroxysulfosuccinimide (sulfo-NHS) solution on an AR2G sensor (ForteBio), 10 μg/mL of human ErbB3 protein solution diluted with 10 mM of sodium acetate (pH 4.0) (ForteBio) was added to immobilize human ErbB3 protein onto the AR2G sensor. The AR2G sensor to which the human ErbB3 protein was immobilized was treated with 1 M of ethanolamine (ForteBio) to inactivate the remaining unreacted carboxyl groups. 12.5 nM, 25 nM, and 50 nM antibody solutions were each added onto the AR2G sensor and then the binding phase of the reaction product was observed for about 900 seconds. Next, a 1x kinetics buffer (ForteBio) was added to the reaction product, and the dissociation phase of the reaction product was observed for about 1200 seconds, followed by determination of an association constant (ka), a dissociation constant (kd), and an equilibrium dissociation constant (KD) of each type of antibody with Octet® analysis software (Pall Life® Sciences).

[Table 3]

Antibody	KD (M)	ka(1/Ms)	kd(1/s)
442P	2.83E-10	1.25E+06	3.52E-04
442S1	<1.0E-12	5.22E+05	3.94E-07
442S2	7.11E-11	1.17E+06	8.28E-05
442S4	3.71E-11	1.48E+06	5.47E-05
442S5	1.75E-11	1.57E+06	2.74E-05
442S6	<1.0E-12	8.72E+05	<1.0E-07
442S9	7.16E-11	8.21 E+05	5.87E-05
442S10	1.14E-10	8.14E+05	9.29E-05
442M3	3.40E-12	7.71E+05	2.62E-06
442M4	<1.0E-12	5.73E+05	<1.0E-07
442M5	<1.0E-12	6.65E+05	<1.0E-07
442M6	2.01 E-11	9.69E+05	1.95E-05
442M7	2.91 E-11	1.56E+06	4.55E-05
442M8	2.56E-12	8.70E+05	2.23E-06
442M10	<1.0E-12	4.71 E+05	<1.0E-07
442M11	5.43E-12	1.49E+06	8.09E-06
472P	2.84E-10	1.79E+06	5.08E-04
472S1	<1.0E-12	6.49E+05	3.33E-07
472S2	<1.0E-12	1.07E+06	<1.0E-07
472S3	<1.0E-12	5.22E+05	1.43E-07
472S4	9.41E-12	1.15E+06	1.09E-05
472M1	1.25E-11	1.39E+06	1.74E-05
451P	5.35E-11	1.18E+06	6.33E-05
451M1	2.48E-11	1.24E+06	3.08E-05
451M2	1.26E-11	1.24E+06	1.56E-05
451M3	<1.0E-12	1.87E+06	2.30E-07

(continued)

Antibody	KD (M)	ka(1/Ms)	kd(1/s)
451M4	6.12E-12	2.01 E+06	1.23E-05
451M5	2.17E-11	1.52E+06	3.29E-05
451M6	3.47E-12	1.20E+06	4.17E-06
451M7	4.92E-12	1.35E+06	6.63E-06

[0051] Referring to Table 3, the selected antibodies were found to have an equilibrium dissociation constant (KD) of about 0.1 nM to about 0.1 pM, indicating high binding affinities to the recombinant human ErbB3 protein.

2. ErbB3 protein-HRG binding inhibitory ability of anti-ErbB3 antibody

[0052] Whether the selected antibodies of Example 1.2 inhibit binding of ErbB3 protein and HRG as a ligand thereof was investigated.

[0053] In particular, a binding affinity of HRG (R&D systems) to human ErbB3 protein (R&D systems) was measured using an Octet® QK384 system (Pall Life Sciences). After 10 μg/mL of HRG protein was immobilized onto an AR2G sensor according to the same method as used in Example 2.1, the remaining unreacted carboxyl groups were inactivated using a 1M ethanolamine (ForteBio). Next, a mixed solution of 5 μg/mL of human ErbB3 protein (R&D systems) and 10 nM or 100 nM of anti-ErbB3 antibodies was added onto the AR2G sensor with the HRG protein immobilized thereon, and then the binding phase was observed for about 900 seconds. A reaction product to which no anti-ErbB3 antibodies were added was used as a negative control group. The amount of the remaining human ErbB3 protein bound to the HRG protein immobilized to the AR2G sensor was measured. A binding affinity (%) of ErbB3 protein and HRG in the presence of the anti-ErbB3 antibodies with respect to the negative control group was calculated. The results are shown in FIG. 2, in which the Y-axis represents a binding affinity (%) relative to the negative control group, and the X-axis represents antibodies at different concentrations of 0 nM, 10 nM, and 100 nM.

[0054] Referring to FIG. 2, the selected antibodies were found to inhibit binding of human ErbB3 protein and HRG protein, depending on the concentrations of the antibodies, whereas the hIgG control group showed no effect on the binding of ErbB3 and HRG.

3. ErbB2-ErbB3 dimerization inhibition ability of anti-ErbB3 antibody

[0055] An investigation was carried out to assess the ability of the selected antibodies of Example 1. 2 to inhibit dimerization of ErbB2 protein and ErbB3 protein.

[0056] In particular, 100 μℓ of recombinant human ErbB2 protein (1 μg/mL) was applied to a multi-array 96-well plate (Thermo scientific) and incubated at 4°C for about 16 hours to coat the ErbB2 protein on the multi-array 96-well plate. 200 μℓ of 5% (w/v) BSA/PBS solution was applied to the coated plate and incubated at 37°C for about 1 hour. A mixture of 50 μℓ of the recombinant human ErbB3 protein (0.6 μg/mL) and 50 μℓ of the selected anti-ErbB3 antibodies (0.2 μg/mL) was applied to the plate and the reaction mixture was incubated at 37°C for about 2 hours. The resulting plate was washed three times with 0.05%(v/v) Tween/PBS solution. 100 μℓ of goat-anti-ErbB3 polyclonal antibody (1 μg/mL, R&D systems) was applied to the washed plate and incubated at 37°C for about 1 hour. The plate was then washed three times with a 0.05%(v/v) Tween/PBS solution. 100 μℓ of anti-goat Fc-horseradish peroxidase (HRP) (Jackson Immunoresearch), diluted at 1:5000 with a 5% (w/v) BSA/PBS solution, was applied to the plate and then incubated at 37°C for about 1 hour. The plate was then washed three times with a 0.05%(v/v) Tween/PBS solution. 100 μℓ of 3,3',5,5'-tetramethylbenzidine (TMB) as a substrate was applied to each well and incubated at room temperature for about 5 minutes, followed by terminating the reaction with 100 μℓ of a 2N sulfuric acid solution. A reaction mixture to which no anti-ErbB3 antibodies were added was used as a negative control group. The absorbance of the plate at a wavelength of 450 nm was measured. The binding affinities of ErbB2 protein and ErbB3 protein under the presence of anti-ErbB3 antibodies were calculated from the measured absorbance. Human IgG, which does not bind to ErbB3, was used as another negative control group.

[0057] The binding affinities (%) of ErbB2 protein and ErbB3 protein in the presence of anti-ErbB3 antibodies with respect to the negative control group were calculated. The results are shown in FIG. 3, wherein the Y-axis denotes a binding affinity (%) relative to the negative control group, and hIgG denotes human IgG.

[0058] Referring to FIG. 3, the selected antibodies were found to inhibit the dimerization of ErbB2 protein and ErbB3 protein, whereas the hIgG control group did not demonstrate any inhibition of dimerization.

4. ErbB3 and Akt phosphorylation inhibition ability of anti-ErbB3 **antibody**

[0059] An investigation was carried out to assess the ability of the selected antibodies of Example 1. 2 to inhibit phosphorylation of ErbB3 protein and Akt.

[0060] In particular, about $5x10^5$ MCF7 breast cancer cells (from the National Institutes of Health) were inoculated onto a 24-well plate, and Roswell Park Memorial Institute (RPMI)-1640 medium (Invitrogen) including penicillin-streptomycin antibiotic (Invitrogen) and 10%(v/v) of fetal bovine serum (FBS) was added to the cells on the 24-well plate and incubated at 37°C under 5% CO_2 conditions for about 24 hours. Next, the medium was exchanged with fresh RPMI-1640 medium, and the cells were cultured under serum starving conditions for about 24 hours. Next, the selected anti-ErbB3 antibodies were added to the cells and incubated at 37°C under 5% CO_2 conditions for about 2 hours. The antibodies 442P and 472P were each added to the cells at concentrations of about 67 nM, 13 nM, 3 nM, 534 pM, 107 pM, 21 pM, and 4 pM, while the antibodies 442S1, 442S5, 442M6, 472S2, and 472M1 were added to the cells at concentrations of 13 nM, 3 nM, 834 pM, 208 pM, 52 pM, and 13 pM. After 1 hours and 45 minutes, HRG was added to the cells and incubated at 37°C under 5% CO_2 conditions for about 15 minutes to stimulate the cells (total antibody treatment time: 2 hours). The cells were washed with cooled PBS and Cell Lysis Solution (Cell Signaling Technology) was added to thereby collect the cells. After quantification of protein in the selected cells was performed by BCA assay, phosphorylation levels of ErbB3 or Akt were analyzed.

[0061] The phosphorylation level of ErbB3 was assayed using a Phospho-ErbB3 Detection Kit (Cell Signaling Technology). After binding the cell protein to an ErbB3 antibody-coated ELISA plate, phosphotyrosine mouse detection antibody and HRP-conjugated anti-mouse antibody were developed on the ELISA plate. Next, tetramethylbenzidine (TMB) substrate was added to the reaction product, the reaction was stopped with reaction stop solution of the kit, and absorbance was measured with a plate reader.

[0062] The phosphorylation level of Akt1 was assayed using a Phospho-Akt1 Detection Kit (Cell Signaling Technology). After binding the cell protein to an anti-phosphoserine-coated ELISA plate, Akt1-specific detection antibody and HRP-conjugated antibody were developed on the ELISA plate. Next, after reaction with TMB substrate, the reaction was stopped with Reaction Stop Solution of the kit, and absorbance was measured with a plate reader.

[0063] FIGS. 4a and 4b are graphs of ErbB3 and Akt phosphorylation ratios, respectively, with respect to antibody concentration, plotted based on the measured absorbance. The half maximal inhibitory concentrations (IC_{50}) of the antibodies were calculated. The results are shown in Table 4.

[Table 4]

Assay	Antibody	IC_{50} (nM)
Inhibition of ErbB3 phosphorylation	442P	1.046
	472P	1.451
	442S1	0.2221
	442S5	0.08537
	442M6	0.271
	472S2	0.1478
	472M1	0.2761
Inhibition of Akt phosphorylation	442S1	0.2393
	442S5	0.1674
	442M6	0.3041
	472S2	0.1953
	472M1	0.2463

[0064] Referring to FIGS. 4a and 4b and Table 4, the selected antibodies were found to inhibit phosphorylation of ErbB3 and Akt.

[0065] Similarly, it was also found that the selected antibodies inhibit phosphorylation of ErbB3 and Akt in breast cancer cell lines MDA-MB-468 and BT474, skin cancer cell line A431, pancreatic cancer cell line BxPC3, head and neck cancer cell line FaDu, lung cancer cell line A549, colorectal cancer cell line LoVo, melanoma cell line MALME-3M, ovarian cancer cell line OVCAR-8, and prostate cancer cell line DU145.

5. Pancreatic cancer cell line BxPC3 proliferation inhibition ability of anti-ErbB3 antibody

[0066] An investigation was carried out to assess the ability of the selected antibodies of Example 1.2 to inhibit proliferation of BxPC3 pancreatic cancer cells.

[0067] In particular, about $1x10^4$ BxPC3 pancreatic cancer cells (American Type Culture Collection) were inoculated onto a 96-well plate, and RPMI-1640 medium (Invitrogen) including 10% FBS was added to the cells on the 96-well plate and incubated at 37°C under 5% CO_2 conditions for about 24 hours. Next, the medium was exchanged with an RPMI-1640 medium including 0.1%(v/v) FBS. 0.02 μg/mL, 0.2 μg/mL, 2 μg/mL, and 20 μg/mL of the 442S1 antibody or 442M6 antibody were added to the incubated cells and cultured at 37°C under 5% CO_2 conditions for about 2 hours. 50 ng/mL of HRG was further added to the cultured cells and incubated at 37°C under 5% CO_2 conditions for about 120 hours. Cultured cells without added antibodies were used as a negative control group. The number of viable cells was measured using a CellTiter-Glo Luminescent Cell Viability Assay (Promega). The relative proliferation rates were calculated based on the measured results. The results are shown in FIG. 5.

[0068] Referring to FIG. 5, the selected antibodies were found to inhibit proliferation of BxPC3 pancreatic cancer cells in a concentration-dependent manner.

Example 3. *in-vivo* effect of anti-ErbB3 antibody

1. Tumor growth inhibition using BT474 breast cancer xenograft model

[0069] An investigation was carried to assess the ability of the selected antibodies of Example 1.2 to inhibit growth of tumors in a breast cancer cell xenograft animal model.

[0070] In particular, human breast cancer BT474 cells (American Type Culture Collection) were cultured in Dulbecco's Modified Eagle's *medium* (DMEM) medium (Hyclone) including 10% FBS. 17 β-estradiol-sustained release pellets (0.36 mg/60 days, Innovative Research of America) were subcutaneously inoculated into female NOD/SCID mice (HFK Bio-Technology Co. Ltd.) one day before the inoculation of cancer cells to maintain blood estrogen level. About $1x10^7$ of BT474 cancer cells were suspended in 100 μℓ of PBS containing 50% Matrigel, and the suspended cancer cells were injected into the fat tissue under a nipple of each mouse. Weights of the mice were measured twice a week, and the tumor volume was calculated using the equation of "0.5 a x b^2", where a and b were the long and short diameters of the tumor, respectively. When the tumor volume reached about 210 mm^3 after 7 days from the inoculation of the cancer cells, the mice were randomly assigned to 7 groups, each including 10 mice. PBS (negative control group), antibodies 442P, 442S1, 442S5, 442M6, 472S2, and 472M1 were administered into the tail veins of the mice in each group twice a week at a dose of 10 mg/kg of body weight for 4 weeks. After the inoculation of the cancer cells, the tumor volume after the administration of the antibodies was calculated. The results are shown in FIG. 6.

[0071] Referring to FIG. 6, it was found that the tumor volume was reduced by the administration of the antibodies relative to the negative control group, and the selected antibodies inhibited tumor growth.

2. Tumor growth inhibition using MDA-MB-468 breast cancer xenograft model

[0072] Human breast cancer cells MDA-MB-468 (American Type Culture Collection) were incubated in an L-15 medium (Hyclone) including 10%(v/v) of fetal bovine serum. About $5x10^6$ cancer cells were suspended in 100 μℓ of PBS including 50% Matrigel and subcutaneously injected into the flank region of female Nu/Nu mice (Vital River laboratories, Ltd). Weights of the mice were measured twice a week, and a tumor volume was calculated using the equation of "0.5 a x b^2", where a and b were the long and short diameters of the tumor, respectively. When the tumor volume reached about 210 mm^3 after 7 days from the injection of the cancer cells, the mice were randomly assigned to 7 groups, each including 10 mice. PBS (negative control group), antibodies 442P, 442S1, 442S5, 442M6, 472S2, and 472M1 were administered into the tail veins of the mice in each group twice a week at a dose of 10 mg/kg of body weight for 4 weeks. After the inoculation of the cancer cells, the tumor volume after the administration of the antibodies was calculated. The results are shown in FIG. 7.

[0073] Referring to FIG. 7, it was found that the tumor volume was reduced by the administration of the antibodies relative to the negative control group, and the selected antibodies inhibited tumor growth.

3. **Tumor** growth inhibition using A431 skin cancer xenograft model

[0074] Human skin cancer A431 cells (American Type Culture Collection) were incubated in DMEM medium (Hyclone) including 10% FBS. About $5x10^6$ cancer cells were suspended in 100 μℓ of PBS including 50% of Matrigel and subcutaneously injected into the flank region of female Balb/c nude mice (HFK Bio-Technology Co. Ltd.). Weights of the mice were measured twice a week, and a tumor volume was calculated using the equation of "0.5 a x b^2", where a and b

were the long and short diameters of the tumor, respectively. When the tumor volume reached about 160 mm^3 after 7 days from the inoculation of the cancer cells, the mice were randomly assigned to 7 groups, each including 10 mice. PBS (negative control group), antibodies 442P, 442S1, 442S5, 442M6, 472S2, and 472M1 were administered into the tail veins of the mice in each group twice a week at a dose of 10 mg/kg of body weight for 4 weeks. After the inoculation of the cancer cells, the tumor volume after the administration of the antibodies was calculated. The results are shown in FIG. 8.

[0075] Referring to FIG. 8, it was found that the tumor volume was reduced by the administration of the antibodies relative to the negative control group, and the selected antibodies inhibited tumor growth.

4. Tumor growth inhibition using tumor xenograft model

[0076] The antibody 442S1 was administered into FaDu head and neck cancer, pancreatic cancer, or lung cancer animal model, and the antibodies 442P or 472P antibodies were administered into gastric cancer animal model, in the same manner as described in Examples 3.1 to 3.3. As a result, it was found that the tumor volume was reduced by the administration of the antibodies relative to the negative control group, and the selected antibodies inhibited tumor growth.

Example 4. Effect of combined administration of anti-cancer drug and anti-ErbB3 antibody

[0077] An investigation was carried out to assess the ability of combined use of the antibodies 442S1 and Cetuximab to improve anti-cancer effects in FaDu head and neck cancer model.

[0078] Human head and neck cancer FaDu cells (Shanghai Institutes for Biological Sciences) were incubated in EMEM medium (Hyclone) including 10% FBS. About $5x10^6$ cancer cells were suspended in 100 $\mu\ell$ of PBS including 50% Matrigel and subcutaneously injected into the flank region of the female NOD/SCID mice (HFK Bio-Technology Co. Ltd). Weights of the mice were measured twice a week, and a tumor volume was calculated using the equation of "0.5 *a* x b^2", where *a* and *b* were the long and short diameters of the tumor, respectively. When the tumor volume reached about 150 mm^3 after 7 days from the inoculation of the cancer cells, the mice were randomly assigned to 4 groups, each including 10 mice. PBS (negative control group), antibodies 442S1 and Cetuximab (Merck) were administered into the tail veins of the mice in each group twice a week at a dose of 5 mg/kg of body weight for 4 weeks. In a combined use treatment group, antibodies 442S1 and Cetuximab were administered into the tail veins of the mice twice a week at a dose of 5 mg/kg of body weight for 4 weeks. Then, no antibodies were administered for one week. The tumor sizes were measured twice a week. The volume of the tumors after the administration of the antibodies or the combined administration was calculated. The results are shown in FIG. 9, in which down arrows (↓) denote time injecting cancer cells, and *** denotes results of Tukey's multiple comparison test after one-way ANOVA ($p<0.001$).

[0079] Referring to FIG. 9, in the combined use of antibodies 442S1 and Cetuximab treatment group, the tumor volume was reduced from the initial administration stage and was about 68 mm^3 on average at the end of the test (n=10/group). Accordingly, the combined administration of the selected antibody and Cetuximab was found to improve anti-cancer efficacy.

Example 5. Anti-cancer drug resistance improvement effect of anti-ErbB3 antibody

1. Paclitaxel resistance improvement effect in breast cancer

[0080] Apoptotic effects of Paclitaxel in breast cancer cell line ZR-75-30 may be reduced in the presence of HRG due to the activation of an ErbB3 signal transduction pathway (Wang S. et al., Oncogene, 29, 4225-4236, 2010). An investigation was carried out to assess the ability of the screened antibodies to improve resistance to Paclitaxel used as an anti-cancer drug and impart an anti-cancer effect.

[0081] About $1x10^4$ ZR-75-30 cells (American Type Culture Collection) were inoculated onto a plate and incubated in RPMI 1640 medium (Invitrogen) including 10%(v/v) FBS at 37°C under 5% CO_2 conditions for about 24 hours. The medium was then exchanged with fresh medium (100 ng/mL HRG added) including 0.1%(v/v) FBS, and further incubation was performed at 37°C under 5% CO_2 conditions for about 24 hours. 10 nM of Paclitaxel (Bristol-Myers Squibb) and 25 μg/mL of antibody 442S1 were added to the cultured cells and incubated at 37°C under 5% CO_2 conditions for about 72 hours. The cultured cells were collected, and the activity of caspase 3/7 as an apoptotic marker was measured using a Caspase 3/7 Substrate Assay (Promega). The measured activity of caspase 3/7 is shown in FIG. 10, in which RLU denotes relative luminescence units, and ** denotes t-test results ($p < 0.01$).

[0082] Referring to FIG. 10, the activity of caspase 3/7 was reduced by Paclitaxel, but was improved by the combined treatment of Paclitaxel and antibody 442S1, compared with the treatment with Paclitaxel alone (n=3). Accordingly, it was found that the apoptotic effect of Paclitaxel may be reduced in the presence of HRG, but recovered by administration of antibody 442S1.

2. Cetuximab resistance improvement effect in colorectal cancer

[0083] Cetuximab is effective in suppressing cancer cell proliferation in DiFi colorectal cancer cells, but loses its efficacy in the presence of HRG due to the activation of an ErbB3 signal transduction pathway. An investigation was carried out to assess the ability of the screened antibodies to overcome resistance to Cetuximab and impart cancer cell proliferation suppression effects.

[0084] In particular, DiFi colon cancer cells were incubated in RPMI-1640 medium (Invitrogen) including an antibiotic (Penicillin-Streptomycin, Invitrogen) and 10% FBS. About $1x10^4$ DiFi cells were inoculated onto a 96-well plate and incubated at 37°C under 5% CO_2 conditions for about 24 hours. Cetuximab and anti-ErbB3 antibody were mixed together in equal concentrations of 200 μg/mL to obtain an Cetuximab/anti-ErbB3 antibody solution, which was then mixed with an equal amount of HRG (40 ng/mL). The Cetuximab/anti-ErbB3 antibody/HRG solution was applied to a 96-well plate and incubated at 37°C under 5% CO_2 conditions for about 72 hours. Cells cultured without antibodies and HRG were used as a negative control group. The number of viable cells was measured using a CellTiter-Glo luminescent cell viability assay (Promega). Cell proliferation rates were calculated based on the measured results. The results are shown in FIG. 11, in which *** denotes t-test results (p<0.001).

[0085] Referring to FIG. 11, the cell proliferation suppression effect of Cetuximab was reduced in the presence of HRG, but recovered in the treatment group which received Cetuximab and 442S1 antibodies in combination. Accordingly, it was found that the cell proliferation suppression effect of Cetuximab may be reduced in the presence of HRG, i.e., an ErbB3 ligand, but may be recovered by 442S1 antibodies blocking the HRG-ErbB3 signaling pathway.

3. Improvement in resistance to Cetuximab in Cetuximab resistant xenograft model

[0086] FaDu human head and neck cancer cells (Shanghai Institutes of Biological Sciences) were incubated in EMEM medium (Hyclone) including 10% FBS (Invitrogen), 0.01 mM NEAA (Non-Essential Amino Acid, Hyclone), and 2 mM L-glutamine (Invitrogen). About $5x10^6$ FaDu cancer cells were suspended in 100 $\mu\ell$ of PBS and then subcutaneously injected into the frank region of the female NOD SCID mice (HFK Bio-Technology Co., Ltd.). Weights of the mice were measured twice a week, and tumor volume was calculated using the equation of "0.5 a x b^2", where a and b were the long and short diameters of the tumor, respectively. When the tumor volume reached about 165 mm^3 after 8 days from the inoculation of the cancer cells, the mice were randomly selected. PBS (negative control group) or Cetuximab was administered into the tail veins of the mice in each group twice a week at a dose of 5 mg/kg of weight for 6.5 weeks. When the tumor growth suppression effect of Cetuximab was not maintained such that tumor volume increased to about 840 mm^3, ten mice were randomly selected from each group, and 5 mg/kg of Cetuximab, 10 mg/kg of antibody 442S1 or combination of 5 mg/kg of Cetuximab and 10 mg/kg of antibody 442S1 was administered to the mice twice a week for 2 weeks. Tumor volumes were measured twice a week. The results are shown in FIG. 12.

[0087] Referring to FIG. 12, it was found that a significant tumor suppression effect was observed in the treatment group that received antibody 442S1 alone or antibody 442S1 and Cetuximab in combination, compared with the treatment group that received Cetuximab alone, indicating that antibody 442S1 may overcome resistance to Cetuximab and suppress tumor growth.

[0088] As described above, according to the one or more example embodiments, an antibody that specifically binds to ErbB3 or an antigen-binding fragment thereof, and use thereof, are provided. The antibody that specifically binds to ErbB3 or an antigen-binding fragment thereof may be effectively used to prevent or treat a disease related to activation or overexpression of ErbB3 protein.

[0089] It should be understood that example embodiments described herein should be considered in a descriptive sense only and not for purposes of limitation. Descriptions of features or aspects within each example embodiment should typically be considered as available for other similar features or aspects in other embodiments.

<110> ISU ABXIS

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<130> I13290WOEP-A

<150> KR 2015 0173281
<151> 2015-12-07

<160> 103

<170> KopatentIn 2.0

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Glu	Val	Gln	Leu	Leu	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
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Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Asp	Tyr
			20					25					30		
Asp	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			
Ser	Ser	Ile	Tyr	Pro	Asp	Ser	Gly	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val
	50					55					60				
Gln	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
65					70					75					80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Lys	Asp	Leu	His	Met	Gly	Pro	Glu	Gly	Pro	Phe	Asp	Tyr	Trp	Gly
			100					105					110		
Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser							
		115					120								

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<223> Heavy chain variable region of antibody 442S1

<400> 2

Glu	Val	Gln	Leu	Leu	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1				5					10						15
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Asp	Tyr
			20					25					30		

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Asp Leu Asp Ser Gly Ser Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Leu His Met Gly Pro Glu Gly Pro Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 3
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<223> Heavy chain variable region of antibody 442S2

<400> 3
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Tyr Pro Asp Ser Gly Ser Thr Asp Tyr Ala Asp Ser Val
50 55 60

Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Leu His Met Gly Pro Glu Gly Pro Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 4
<211> 121
<212> PRT
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<220>
<223> Heavy chain variable region of antibody 442S4

<400> 4
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Glu Pro Asp Phe Gly Ser Ser Tyr Tyr Ala Asp Ser Val
50 55 60

Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Leu His Met Gly Pro Glu Gly Pro Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 5
<211> 121
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<220>
<223> Heavy chain variable region of antibody 442S5

<400> 5
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ile Ile Glu Pro Asp Ser Gly Ser Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Leu His Met Gly Pro Glu Gly Pro Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 6

<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Heavy chain variable region of antibody 442S6

<400> 6

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 1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Tyr Pro Asp Ser Gly Ser Thr Asp Tyr Ala Asp Ser Val
    50                  55                  60

Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Asp Arg His Met Trp Pro Glu Gly Pro Phe Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
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<220>
<223> Heavy chain variable region of antibody 442S9

<400> 7

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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Tyr Pro Asp Ser Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Asp Arg His Met Trp Pro Glu Gly Pro Phe Asp Tyr Trp Gly
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100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 8
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<220>
<223> Heavy chain variable region of antibody 442S10

<400> 8
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Tyr Pro Asp Ser Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Arg His Met Trp Pro Glu Gly Pro Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 9
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Heavy chain variable region of antibody 442M3

<400> 9
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Tyr Pro Asp Ser Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Arg His Met Trp Pro Glu Gly Pro Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 10
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Heavy chain variable region of antibody 442M4

<400> 10
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Asp Leu Asp Ser Gly Ser Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Leu His Met Gly Pro Glu Gly Pro Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 11
<211> 121
<212> PRT
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<220>
<223> Heavy chain variable region of antibody 442M5

<400> 11
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Asp Leu Asp Ser Gly Ser Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Leu His Met Gly Pro Glu Gly Pro Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 12
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Heavy chain variable region of antibody 442M6

<400> 12
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Glu Pro Asp Ser Gly Ser Thr Asp Tyr Ala Asp Ser Val
50 55 60

Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Arg His Met Trp Pro Glu Gly Pro Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 13
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Heavy chain variable region of antibody 442M7

<400> 13
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Glu Pro Asp Ser Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Gln Ser Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Leu His Met Gly Pro Glu Gly Pro Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 14
<211> 121
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<223> Heavy chain variable region of antibody 442M8

<400> 14
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Tyr Pro Asp Ser Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Leu His Met Gly Pro Glu Gly Pro Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 15

<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Heavy chain variable region of antibody 442M10

<400> 15
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1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Tyr Pro Asp Ser Gly Ser Thr Asp Tyr Ala Asp Ser Val
50 55 60

Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Leu His Met Trp Pro Glu Gly Pro Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 16
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Heavy chain variable region of antibody 442M11

<400> 16
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Glu Pro Asp Tyr Gly Ser Thr Leu Tyr Ala Asp Ser Val
50 55 60

Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Leu His Met Gly Pro Glu Gly Pro Phe Asp Tyr Trp Gly

100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 17
<211> 127
<212> PRT
<213> Artificial Sequence

<220>
<223> Heavy chain variable region of antibody 472P

<400> 17
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Tyr Asp Gly Gly Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Pro Ser Trp Cys Leu Gln Asp Leu Cys Tyr Tyr Ala Asp
100 105 110

Gly Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 18
<211> 127
<212> PRT
<213> Artificial Sequence

<220>
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<400> 18
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1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Trp Tyr
20 25 30

Asp Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Tyr Asp Gly Gly Asn Thr Tyr Tyr Ala Asp Ser Val

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     50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                 85                  90                  95

Ala Arg Asp Pro Ser Trp Cys Leu Gln Asp Leu Cys Tyr Tyr Ala Asp
            100                 105                 110

Gly Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125
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<210> 19
<211> 127
<212> PRT
<213> Artificial Sequence

<220>
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<400> 19

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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Trp Tyr
             20                  25                  30

Asp Leu Ala Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
         35                  40                  45

Ser Gly Ile Ser Tyr Asp Gly Gly Asn Thr Tyr Tyr Ala Asp Ser Val
     50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                 85                  90                  95

Ala Arg Asp Pro Ser Trp Cys Leu Gln Asp Leu Cys Tyr Tyr Ala Asp
            100                 105                 110

Gly Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125
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<211> 127
<212> PRT
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<220>
<223> Heavy chain variable region of antibody 472S3

<400> 20
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Trp Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Tyr Asp Gly Gly Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Pro Ser Trp Cys Leu Gln Asp Leu Cys Tyr Tyr Ala Asp
100 105 110

Gly Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 21
<211> 127
<212> PRT
<213> Artificial Sequence

<220>
<223> Heavy chain variable region of antibody 472S4

<400> 21
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Trp Tyr
20 25 30

Asp Ile Ala Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Tyr Asp Gly Gly Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Pro Ser Trp Cys Leu Gln Asp Leu Cys Tyr Tyr Ala Asp
100 105 110

Gly Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 22
<211> 127
<212> PRT
<213> Artificial Sequence

<220>
<223> Heavy chain variable region of antibody 472M1

<400> 22

Glu	Val	Gln	Leu	Leu	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1				5				10						15	
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Trp	Tyr
			20					25					30		
Asp	Leu	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			
Ser	Gly	Ile	Ser	Tyr	Asp	Gly	Gly	Asn	Thr	Tyr	Tyr	Ala	Asp	Ser	Val
	50					55					60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
65					70					75					80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Asp	Pro	Ser	Trp	Cys	Leu	Gln	Asp	Leu	Cys	Tyr	Tyr	Ala	Asp
			100					105					110		
Gly	Met	Asp	Val	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	
		115					120					125			

<210> 23
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Heavy chain variable region of antibody 451P

<400> 23

Glu	Val	Gln	Leu	Leu	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1				5				10						15	
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Asp	Tyr
			20					25					30		
Asp	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			
Ser	Ala	Ile	Tyr	Tyr	Asp	Ser	Gly	Ser	Ile	Tyr	Tyr	Ala	Asp	Ser	Ala
	50					55					60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
65					70					75					80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Arg Leu Phe Val Ser Asp Ser Thr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 24
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Heavy chain variable region of antibody 451M1

<400> 24
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Tyr Tyr Asp Ser Gly Ser Ile Tyr Tyr Ala Asp Ser Ala
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Arg Leu Phe Met Ser Asp Ser Thr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 25
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Heavy chain variable region of antibody 451M2

<400> 25
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

35 40 45

Ser Ala Ile Tyr Tyr Asp Ser Gly Ser Ile Tyr Tyr Ala Asp Ser Ala
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Arg Leu Phe Ala Ser Asp Ser Thr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 26
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Heavy chain variable region of antibody 451M3

<400> 26
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser His Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Tyr Tyr Asp Ser Gly Ser Ile Tyr Tyr Ala Asp Ser Ala
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Arg Leu Phe Ala Ser Asp Ser Thr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 27
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Heavy chain variable region of antibody 451M4

<400> 27

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Tyr Tyr
            20                  25                  30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Tyr Tyr Asp Ser Gly Ser Ile Tyr Tyr Ala Asp Ser Ala
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Asp Arg Leu Phe Ala Ser Asp Ser Thr Phe Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 28
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Heavy chain variable region of antibody 451M5

<400> 28

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Tyr Tyr Asp Ser Gly Ser Ile Tyr Tyr Ala Asp Ser Ala
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Asp Arg Leu Phe Glu Ser Asp Ser Thr Phe Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 29
<211> 121
<212> PRT

<213> Artificial Sequence

<220>
<223> Heavy chain variable region of antibody 451M6

<400> 29
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser His Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Tyr Tyr Asp Ser Gly Ser Ile Tyr Tyr Ala Asp Ser Ala
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Arg Leu Phe Glu Ser Asp Ser Thr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 30
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Heavy chain variable region of antibody 451M7

<400> 30
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Tyr Tyr
20 25 30

Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Tyr Tyr Asp Ser Gly Ser Ile Tyr Tyr Ala Asp Ser Ala
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Arg Leu Phe Glu Ser Asp Ser Thr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 31
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain variable region of antibody 442P

<400> 31
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Ser Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ser Asp Asn His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Ser Ser Leu
85 90 95

Ser Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 32
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain variable region of antibody 442S1

<400> 32
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Ser Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ser Asp Asn His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Gly Trp Asp Thr Ser Leu
85 90 95

Ser Gly His Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 33
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain variable region of antibody 442S2

<400> 33
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Ser Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ser Asp Asn His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Ser Ser Leu
85 90 95

Ser Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 34
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain variable region of antibody 442S4

<400> 34
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Ser Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ser Asp Asn His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Ser Ser Leu

85 90 95

Ser Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 35
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain variable region of antibody 442S5

<400> 35
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Ser Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ser Asp Asn His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Ser Ser Leu
85 90 95

Ser Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 36
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain variable region of antibody 442S6

<400> 36
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Ser Gly Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ala Asp Asn Trp Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Ser Ser Leu
85 90 95

Ser Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 37
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain variable region of antibody 442S9

<400> 37
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Ser Gly Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ala Asp Asn His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Ser Ser Leu
85 90 95

Ser Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 38
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain variable region of antibody 442S10

<400> 38
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Ser Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ser Asp Asn His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Ser Ser Leu
85 90 95

Ser Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 39
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain variable region of antibody 442M3

<400> 39
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Ser Gly Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ala Asp Asn Trp Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Ser Ser Leu
85 90 95

Ser Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 40
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain variable region of antibody 442M4

<400> 40
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Ser Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ser Asp Asn His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg

65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Val Gly Trp Asp Ser Ser Leu
85 90 95

Tyr Gly His Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 41
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain variable region of antibody 442M5

<400> 41
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Ser Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ser Asp Asn His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys His Ala Trp Asp Ser Ser Leu
85 90 95

Trp Gly Asp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 42
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain variable region of antibody 442M6

<400> 42
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Ser Gly Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ala Asp Asn Trp Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Ser Ser Leu
85 90 95

Ser Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 43
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain variable region of antibody 442M7

<400> 43
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Ser Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ser Asp Asn His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Ser Ser Leu
85 90 95

Ser Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 44
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain variable region of antibody 442M8

<400> 44
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Ser Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ser Asp Asn His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys His Ala Trp Asp Ser Ser Leu
85 90 95

Tyr Val Asp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 45
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain variable region of antibody 442M10

<400> 45
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Ser Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ala Asp Asn Phe Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Ser Ser Leu
85 90 95

Ser Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 46
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain variable region of antibody 442M11

<400> 46
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Ser Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ser Asp Asn His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser

50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys His Ala Trp Asp Ser Ser Leu
85 90 95

Ser Gly Asp Phe Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 47
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain variable region of antibody 472P

<400> 47
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Ser Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ala Asp Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Trp Asp Tyr Ser Leu
85 90 95

Ser Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 48
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain variable region of antibody 472S1

<400> 48
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Ser Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ala Asp Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Trp Asp Tyr Ser Leu
85 90 95

Ser Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 49
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain variable region of antibody 472S2

<400> 49
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Ser Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ala Asp Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Trp Asp Tyr Ser Leu
85 90 95

Ser Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 50
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain variable region of antibody 472S3

<400> 50
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Ser Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ala Asp Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Trp Asp Tyr Ser Leu
85 90 95

Ser Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 51
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain variable region of antibody 472S4

<400> 51
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Ser Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ala Asp Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Trp Asp Tyr Ser Leu
85 90 95

Ser Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 52
<211> 111
<212> PRT
<213> Artificial Sequence

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<400> 52
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Ser Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu

35 40 45

Ile Tyr Ala Asp Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Trp Asp Tyr Ser Leu
85 90 95

Ser Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 53
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<223> Light chain variable region of antibody 451P

<400> 53
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Pro Ser Asn Ile Gly Asn Asn
20 25 30

Ser Val Thr Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Tyr Asp Ser His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Trp Asp Ala Ser Leu
85 90 95

Asn Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 54
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<400> 54
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Pro Ser Asn Ile Gly Asn Asn
20 25 30

Ser Val Thr Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Tyr Asp Ser His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Trp Asp Ala Ser Leu
85 90 95

Asn Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 55
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Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Pro Ser Asn Ile Gly Asn Asn
20 25 30

Ser Val Thr Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Tyr Asp Ser His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Trp Asp Ala Ser Leu
85 90 95

Asn Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 56
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1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Pro Ser Asn Ile Gly Asn Asn
20 25 30

Ser Val Thr Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Tyr Asp Ser His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Trp Asp Ala Ser Leu
85 90 95

Asn Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 57
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<400> 57
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1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Pro Ser Asn Ile Gly Asn Asn
20 25 30

Ser Val Thr Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Tyr Asp Ser His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Trp Asp Ala Ser Leu
85 90 95

Asn Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 58
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<220>
<223> Light chain variable region of antibody 451M5

<400> 58
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Pro Ser Asn Ile Gly Asn Asn

20 25 30

Ser Val Thr Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Tyr Asp Ser His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Trp Asp Ala Ser Leu
85 90 95

Asn Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

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Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Pro Ser Asn Ile Gly Asn Asn
20 25 30

Ser Val Thr Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Tyr Asp Ser His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Trp Asp Ala Ser Leu
85 90 95

Asn Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 60
<211> 111
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<220>
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Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Pro Ser Asn Ile Gly Asn Asn
20 25 30

Ser Val Thr Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Tyr Asp Ser His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Trp Asp Ala Ser Leu
85 90 95

Asn Gly Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 61
<211> 5
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<400> 61
Asp Tyr Asp Met Ser
1 5

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<400> 62
Trp Tyr Asp Met Thr
1 5

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<400> 63
Trp Tyr Asp Leu Ala
1 5

<210> 64
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<400> 64
Trp Tyr Asp Met Ser
1 5

<210> 65
<211> 5
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<400> 65
Trp Tyr Asp Ile Ala
1 5

<210> 66
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<400> 66
Trp Tyr Asp Leu Ser
1 5

<210> 67
<211> 5
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<400> 67
His Tyr Asp Met Ser
1 5

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<211> 5
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<400> 68
Tyr Tyr Asp Met Ser
1 5

<210> 69
<211> 17
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<400> 69
Ser Ile Tyr Pro Asp Ser Gly Ser Thr Tyr Tyr Ala Asp Ser Val Gln
1 5 10 15

Gly

<210> 70
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<220>
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<400> 70
Thr Ile Asp Leu Asp Ser Gly Ser Ile Tyr Tyr Ala Asp Ser Val Gln
1 5 10 15

Gly

<210> 71
<211> 17
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<400> 71
Ser Ile Tyr Pro Asp Ser Gly Ser Thr Asp Tyr Ala Asp Ser Val Gln
1 5 10 15

Gly

<210> 72
<211> 17
<212> PRT
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<220>
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<400> 72
Ser Ile Glu Pro Asp Phe Gly Ser Ser Tyr Tyr Ala Asp Ser Val Arg
1 5 10 15

Gly

<210> 73
<211> 17
<212> PRT
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<220>
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<400> 73
Ile Ile Glu Pro Asp Ser Gly Ser Ile Tyr Tyr Ala Asp Ser Val Gln
1 5 10 15

Gly

<210> 74
<211> 17
<212> PRT
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<220>
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<400> 74
Ser Ile Glu Pro Asp Ser Gly Ser Thr Asp Tyr Ala Asp Ser Val Gln
1 5 10 15

Gly

<210> 75
<211> 17
<212> PRT
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<220>
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<400> 75
Thr Ile Glu Pro Asp Ser Gly Ser Thr Tyr Tyr Ala Asp Ser Val Gln
1 5 10 15

Ser

<210> 76
<211> 17

<212> PRT
<213> Artificial Sequence

<220>
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<400> 76
Gly Ile Ser Tyr Asp Gly Gly Asn Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 77
<211> 17
<212> PRT
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<220>
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<400> 77
Ala Ile Tyr Tyr Asp Ser Gly Ser Ile Tyr Tyr Ala Asp Ser Ala Lys
1 5 10 15

Gly

<210> 78
<211> 12
<212> PRT
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<220>
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Asp Leu His Met Gly Pro Glu Gly Pro Phe Asp Tyr
1 5 10

<210> 79
<211> 12
<212> PRT
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<400> 79
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1 5 10

<210> 80
<211> 12
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<400> 80
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1 5 10

<210> 81
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1 5 10 15

Asp Val

<210> 82
<211> 12
<212> PRT
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<220>
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<400> 82
Asp Arg Leu Phe Val Ser Asp Ser Thr Phe Asp Tyr
1 5 10

<210> 83
<211> 12
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<220>
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<400> 83
Asp Arg Leu Phe Met Ser Asp Ser Thr Phe Asp Tyr
1 5 10

<210> 84
<211> 12
<212> PRT
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<220>
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<400> 84
Asp Arg Leu Phe Ala Ser Asp Ser Thr Phe Asp Tyr
1 5 10

<210> 85
<211> 12
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<220>
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<400> 85
Asp Arg Leu Phe Glu Ser Asp Ser Thr Phe Asp Tyr
1 5 10

<210> 86
<211> 13
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<220>
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<400> 86
Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Ser Val Ser
1 5 10

<210> 87
<211> 13
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<400> 87
Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Ser Gly Ser
1 5 10

<210> 88
<211> 7
<212> PRT
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<220>
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<400> 88
Ser Asp Asn His Arg Pro Ser
1 5

<210> 89
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<220>
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<400> 89
Ala Asp Asn Trp Arg Pro Ser
1 5

<210> 90
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<220>
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<400> 90
Ala Asp Asn His Arg Pro Ser
1 5

<210> 91
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<400> 91
Ala Asp Asn Phe Arg Pro Ser
1 5

<210> 92
<211> 7
<212> PRT
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<400> 92
Ala Asp Ser Asn Arg Pro Ser
1 5

<210> 93
<211> 7
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<220>
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<400> 93
Tyr Asp Ser His Arg Pro Ser
1 5

<210> 94
<211> 11
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<400> 94
Ala Ala Trp Asp Ser Ser Leu Ser Gly Tyr Val
1 5 10

<210> 95
<211> 11
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<220>
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<400> 95
Gln Gly Trp Asp Thr Ser Leu Ser Gly His Val
1 5 10

<210> 96
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Val Gly Trp Asp Ser Ser Leu Tyr Gly His Val
1 5 10

<210> 97
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His Ala Trp Asp Ser Ser Leu Trp Gly Asp Val
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<210> 98
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His Ala Trp Asp Ser Ser Leu Tyr Val Asp Val
1 5 10

<210> 99
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<400> 99
His Ala Trp Asp Ser Ser Leu Ser Gly Asp Phe
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Gly Ser Trp Asp Tyr Ser Leu Ser Gly Tyr Val
1 5 10

<210> 101
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<220>
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1 5 10

<210> 102
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<220>
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<400> 102
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1 5 10 15

Gly

<210> 103
<211> 13
<212> PRT
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<220>
<223> Light chain CDR1

<400> 103
Ser Gly Ser Pro Ser Asn Ile Gly Asn Asn Ser Val Thr
1 5 10

Claims

1. A pharmaceutical composition for use in the prevention or treatment of a cancer or anti-cancer drug resistance, the pharmaceutical composition comprising an antibody or an antigen-binding fragment thereof that specifically binds to ErbB3, comprising heavy chain complementarity determining regions (CDR-Hs) and light chain complementarity determining regions (CDR-Ls), wherein the antibody is selected from the group consisting of:

   (1) an antibody comprising a CDR-H1 having the sequence of SEQ ID NO: 61, a CDR-H2 having the sequence of SEQ ID NO: 70, a CDR-H3 having the sequence of SEQ ID NO: 78, a CDR-L1 having the sequence of SEQ ID NO: 86, a CDR-L2 having the sequence of SEQ ID NO: 88, and a CDR-L3 having the sequence of SEQ ID NO: 95;
   (2) an antibody comprising a CDR-H1 having the sequence of SEQ ID NO: 61, a CDR-H2 having the sequence of SEQ ID NO: 73, a CDR-H3 having the sequence of SEQ ID NO: 78, a CDR-L1 having the sequence of SEQ ID NO: 86, a CDR-L2 having the sequence of SEQ ID NO: 88, and a CDR-L3 having the sequence of SEQ ID NO: 94;
   (3) an antibody comprising a CDR-H1 having the sequence of SEQ ID NO: 61, a CDR-H2 having the sequence of SEQ ID NO: 74, a CDR-H3 having the sequence of SEQ ID NO: 79, a CDR-L1 having the sequence of SEQ ID NO: 87, a CDR-L2 having the sequence of SEQ ID NO: 89, and a CDR-L3 having the sequence of SEQ ID NO: 94;
   (4) an antibody comprising a CDR-H1 having the sequence of SEQ ID NO: 63, a CDR-H2 having the sequence of SEQ ID NO: 76, a CDR-H3 having the sequence of SEQ ID NO: 81, a CDR-L1 having the sequence of SEQ ID NO: 86, a CDR-L2 having the sequence of SEQ ID NO: 92, and a CDR-L3 having the sequence of SEQ ID NO: 100;
   (5) an antibody comprising a CDR-H1 having the sequence of SEQ ID NO: 66, a CDR-H2 having the sequence of SEQ ID NO: 76, a CDR-H3 having the sequence of SEQ ID NO: 81, a CDR-L1 having the sequence of SEQ ID NO: 86, a CDR-L2 having the sequence of SEQ ID NO: 92, and a CDR-L3 having the sequence of SEQ ID NO: 100.

2. The pharmaceutical composition of claim 1, wherein the cancer is selected from the group consisting of breast cancer, skin cancer, head and neck cancer, pancreatic cancer, lung cancer, colon cancer, colorectal cancer, gastric cancer, ovarian cancer, prostate cancer, bladder cancer, uterine cancer, liver cancer, kidney cancer, clear cell sarcoma, melanoma, cerebrospinal tumors, brain cancer, thymoma, mesothelioma, esophageal cancer, biliary tract cancer, testicular cancer, germinal cancer, thyroid cancer, parathyroid cancer, cervical cancer, endometrial cancer, lymphoma, myelodysplastic syndromes (MDS), myelofibrosis, acute leukemia, chronic leukemia, multiple myeloma, Hodgkin's disease, endocrine cancer, and sarcoma.

3. The pharmaceutical composition of any one of claims 1 to 2, further comprising an anti-cancer drug.

4. The pharmaceutical composition of claim 3, wherein the anti-cancer drug is Cetuximab, Panitumumab, Erlotinib, Gefitinib, Trastuzumab, T-DM1, Pertuzumab, Lapatinib, Paclitaxel, Tamoxifen, Cisplatin, anti-CTLA-4 antibody, anti-PD-1 antibody, anti-PD-Ll antibody, 5-fluorouracil (5FU), Gemcitabine, or a combination thereof.

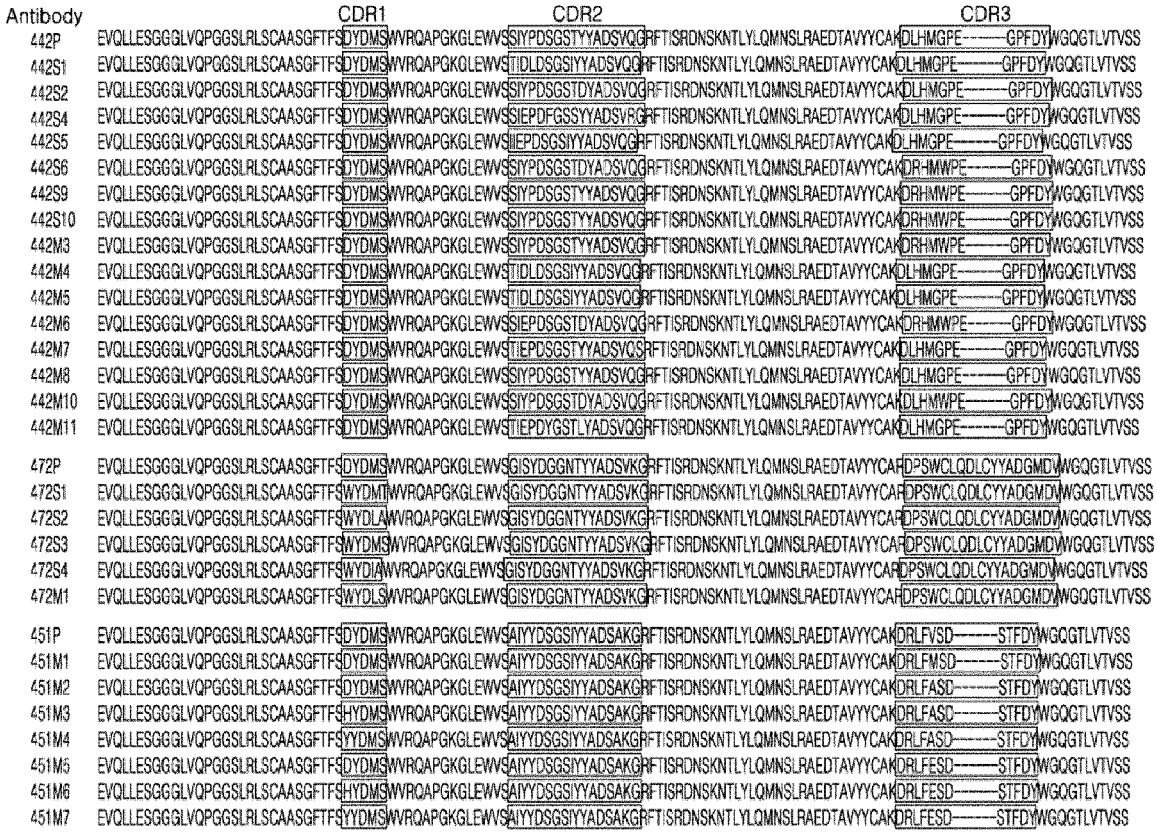
5. The pharmaceutical composition of claim 4, wherein the pharmaceutical composition further comprises a single composition or separate compositions.

6. An antibody or antigen-binding fragment thereof for use in the prevention or treatment of a cancer or anti-cancer drug resistance in an individual, the antibody or the antigen-binding fragment thereof that specifically binds to ErbB3, comprising heavy chain complementarity determining regions (CDR-Hs) and light chain complementarity determining regions (CDR-Ls), wherein the antibody is selected from the group consisting of:

(1) an antibody comprising a CDR-H1 having the sequence of SEQ ID NO: 61, a CDR-H2 having the sequence of SEQ ID NO: 70, a CDR-H3 having the sequence of SEQ ID NO: 78, a CDR-L1 having the sequence of SEQ ID NO: 86, a CDR-L2 having the sequence of SEQ ID NO: 88, and a CDR-L3 having the sequence of SEQ ID NO: 95;
(2) an antibody comprising a CDR-H1 having the sequence of SEQ ID NO: 61, a CDR-H2 having the sequence of SEQ ID NO: 73, a CDR-H3 having the sequence of SEQ ID NO: 78, a CDR-L1 having the sequence of SEQ ID NO: 86, a CDR-L2 having the sequence of SEQ ID NO: 88, and a CDR-L3 having the sequence of SEQ ID NO: 94;
(3) an antibody comprising a CDR-H1 having the sequence of SEQ ID NO: 61, a CDR-H2 having the sequence of SEQ ID NO: 74, a CDR-H3 having the sequence of SEQ ID NO: 79, a CDR-L1 having the sequence of SEQ ID NO: 87, a CDR-L2 having the sequence of SEQ ID NO: 89, and a CDR-L3 having the sequence of SEQ ID NO: 94;
(4) an antibody comprising a CDR-H1 having the sequence of SEQ ID NO: 63, a CDR-H2 having the sequence of SEQ ID NO: 76, a CDR-H3 having the sequence of SEQ ID NO: 81, a CDR-L1 having the sequence of SEQ ID NO: 86, a CDR-L2 having the sequence of SEQ ID NO: 92, and a CDR-L3 having the sequence of SEQ ID NO: 100;
(5) an antibody comprising a CDR-H1 having the sequence of SEQ ID NO: 66, a CDR-H2 having the sequence of SEQ ID NO: 76, a CDR-H3 having the sequence of SEQ ID NO: 81, a CDR-L1 having the sequence of SEQ ID NO: 86, a CDR-L2 having the sequence of SEQ ID NO: 92, and a CDR-L3 having the sequence of SEQ ID NO: 100.

7. The antibody or antigen-binding fragment thereof for use according to claim 6, further comprising administering an anti-cancer drug to the individual.

FIG. 1A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CDR2
CDR3
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442M8 EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYDMSWVRQAPGKGLEWVSSIYPDSGSTYYADSVQGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDLHMGPE------GPFDYWGQGTLVTVSS
442M10 EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYDMSWVRQAPGKGLEWVSSIYPDSGSTDYADSVQGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDLHMWPE------GPFDYWGQGTLVTVSS
442M11 EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYDMSWVRQAPGKGLEWVSTIEPDYGSTLYADSVQGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDLHMGPE------GPFDYWGQGTLVTVSS
472P EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYDMSWVRQAPGKGLEWVSGISYDGGNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDPSWCLQDLCYYADGMDVWGQGTLVTVSS
472S1 EVQLLESGGGLVQPGGSLRLSCAASGFTFSWYDMTWVRQAPGKGLEWVSGISYDGGNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDPSWCLQDLCYYADGMDVWGQGTLVTVSS
472S2 EVQLLESGGGLVQPGGSLRLSCAASGFTFSWYDLAWVRQAPGKGLEWVSGISYDGGNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDPSWCLQDLCYYADGMDVWGQGTLVTVSS
472S3 EVQLLESGGGLVQPGGSLRLSCAASGFTFSWYDMSWVRQAPGKGLEWVSGISYDGGNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDPSWCLQDLCYYADGMDVWGQGTLVTVSS
472S4 EVQLLESGGGLVQPGGSLRLSCAASGFTFSWYDIAWVRQAPGKGLEWVSGISYDGGNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDPSWCLQDLCYYADGMDVWGQGTLVTVSS
472M1 EVQLLESGGGLVQPGGSLRLSCAASGFTFSWYDLSWVRQAPGKGLEWVSGISYDGGNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDPSWCLQDLCYYADGMDVWGQGTLVTVSS
451P EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYDMSWVRQAPGKGLEWVSAIYYDSGSIYYADSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRLFVSD------STFDYWGQGTLVTVSS
451M1 EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYDMSWVRQAPGKGLEWVSAIYYDSGSIYYADSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRLFMSD------STFDYWGQGTLVTVSS
451M2 EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYDMSWVRQAPGKGLEWVSAIYYDSGSIYYADSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRLFASD------STFDYWGQGTLVTVSS
451M3 EVQLLESGGGLVQPGGSLRLSCAASGFTFSHYDMSWVRQAPGKGLEWVSAIYYDSGSIYYADSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRLFASD------STFDYWGQGTLVTVSS
451M4 EVQLLESGGGLVQPGGSLRLSCAASGFTFSYYDMSWVRQAPGKGLEWVSAIYYDSGSIYYADSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRLFASD------STFDYWGQGTLVTVSS
451M5 EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYDMSWVRQAPGKGLEWVSAIYYDSGSIYYADSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRLFESD------STFDYWGQGTLVTVSS
451M6 EVQLLESGGGLVQPGGSLRLSCAASGFTFSHYDMSWVRQAPGKGLEWVSAIYYDSGSIYYADSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRLFESD------STFDYWGQGTLVTVSS
451M7 EVQLLESGGGLVQPGGSLRLSCAASGFTFSYYDMSWVRQAPGKGLEWVSAIYYDSGSIYYADSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRLFESD------STFDYWGQGTLVTVSS

FIG. 1B

Antibody
CDR1
CDR2
CDR3
442P QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSVSWYQQLPGTAPKLLIYSDNHRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDSSLSGYVFGGGTKLTVLG
442S1 QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSVSWYQQLPGTAPKLLIYSDNHRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCQGWDTSLSGHVFGGGTKLTVLG
442S2 QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSVSWYQQLPGTAPKLLIYSDNHRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDSSLSGYVFGGGTKLTVLG
442S4 QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSVSWYQQLPGTAPKLLIYSDNHRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDSSLSGYVFGGGTKLTVLG
442S5 QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSVSWYQQLPGTAPKLLIYSDNHRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDSSLSGYVFGGGTKLTVLG
442S6 QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSGSWYQQLPGTAPKLLIYADNWRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDSSLSGYVFGGGTKLTVLG
442S9 QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSGSWYQQLPGTAPKLLIYADNHRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDSSLSGYVFGGGTKLTVLG
442S10 QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSVSWYQQLPGTAPKLLIYSDNHRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDSSLSGYVFGGGTKLTVLG
442M3 QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSGSWYQQLPGTAPKLLIYADNWRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDSSLSGYVFGGGTKLTVLG
442M4 QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSVSWYQQLPGTAPKLLIYSDNHRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCVGWDSSLYGHVFGGGTKLTVLG
442M5 QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSVSWYQQLPGTAPKLLIYSDNHRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCHAWDSSLWGDVFGGGTKLTVLG
442M6 QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSGSWYQQLPGTAPKLLIYADNWRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDSSLSGYVFGGGTKLTVLG
442M7 QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSVSWYQQLPGTAPKLLIYSDNHRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDSSLSGYVFGGGTKLTVLG
442M8 QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSVSWYQQLPGTAPKLLIYSDNHRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCHAWDSSLYVDVFGGGTKLTVLG
442M10 QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSVSWYQQLPGTAPKLLIYADNFRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDSSLSGYVFGGGTKLTVLG
442M11 QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSVSWYQQLPGTAPKLLIYSDNHRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCHAWDSSLSGDRFGGGTKLTVLG
472P QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSVSWYQQLPGTAPKLLIYADSNRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCGSWDYSLSGYVFGGGTKLTVLG
472S1 QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSVSWYQQLPGTAPKLLIYADSNRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCGSWDYSLSGYVFGGGTKLTVLG
472S2 QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSVSWYQQLPGTAPKLLIYADSNRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCGSWDYSLSGYVFGGGTKLTVLG
472S3 QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSVSWYQQLPGTAPKLLIYADSNRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCGSWDYSLSGYVFGGGTKLTVLG
472S4 QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSVSWYQQLPGTAPKLLIYADSNRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCGSWDYSLSGYVFGGGTKLTVLG
472M1 QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNSVSWYQQLPGTAPKLLIYADSNRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCGSWDYSLSGYVFGGGTKLTVLG
451P QSVLTQPPSASGTPGQRVTISCSGSPSNIGNNSVTWYQQLPGTAPKLLIYYDSHRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCGSWDASLNGYVFGGGTKLTVLG
451M1 QSVLTQPPSASGTPGQRVTISCSGSPSNIGNNSVTWYQQLPGTAPKLLIYYDSHRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCGSWDASLNGYVFGGGTKLTVLG
451M2 QSVLTQPPSASGTPGQRVTISCSGSPSNIGNNSVTWYQQLPGTAPKLLIYYDSHRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCGSWDASLNGYVFGGGTKLTVLG
451M3 QSVLTQPPSASGTPGQRVTISCSGSPSNIGNNSVTWYQQLPGTAPKLLIYYDSHRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCGSWDASLNGYVFGGGTKLTVLG
451M4 QSVLTQPPSASGTPGQRVTISCSGSPSNIGNNSVTWYQQLPGTAPKLLIYYDSHRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCGSWDASLNGYVFGGGTKLTVLG
451M5 QSVLTQPPSASGTPGQRVTISCSGSPSNIGNNSVTWYQQLPGTAPKLLIYYDSHRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCGSWDASLNGYVFGGGTKLTVLG
451M6 QSVLTQPPSASGTPGQRVTISCSGSPSNIGNNSVTWYQQLPGTAPKLLIYYDSHRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCGSWDASLNGYVFGGGTKLTVLG
451M7 QSVLTQPPSASGTPGQRVTISCSGSPSNIGNNSVTWYQQLPGTAPKLLIYYDSHRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCGSWDASLNGYVFGGGTKLTVLG

Figure 2

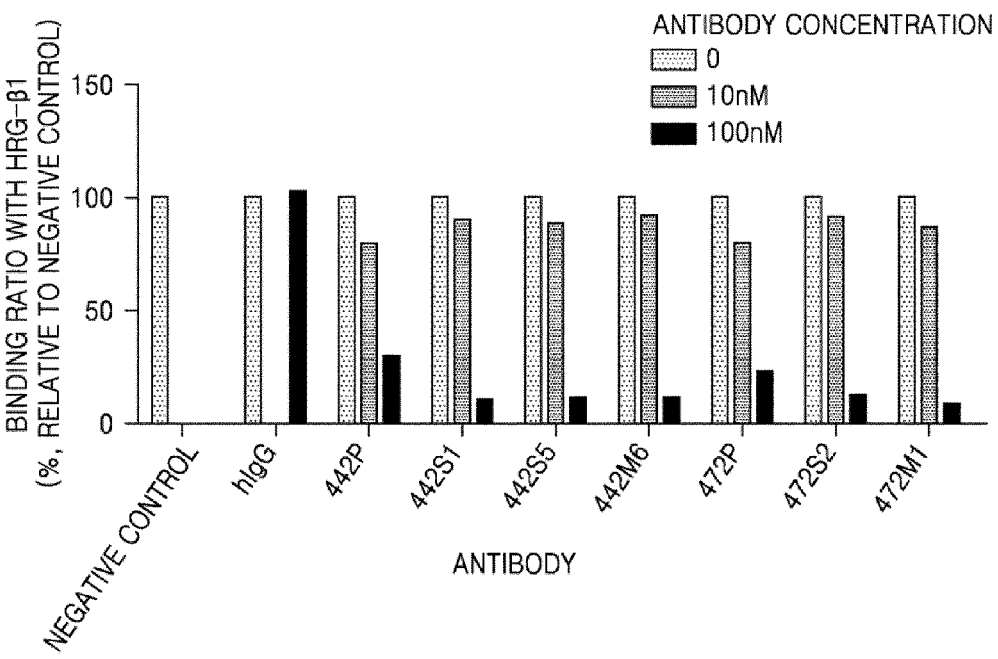

ANTIBODY CONCENTRATION
0
10nM
100nM
BINDING RATIO WITH HRG-β1
(%, RELATIVE TO NEGATIVE CONTROL)
150
100
50
0
NEGATIVE CONTROL
hIgG
442P
442S1
442S5
442M6
472P
472S2
472M1
ANTIBODY

Figure 3

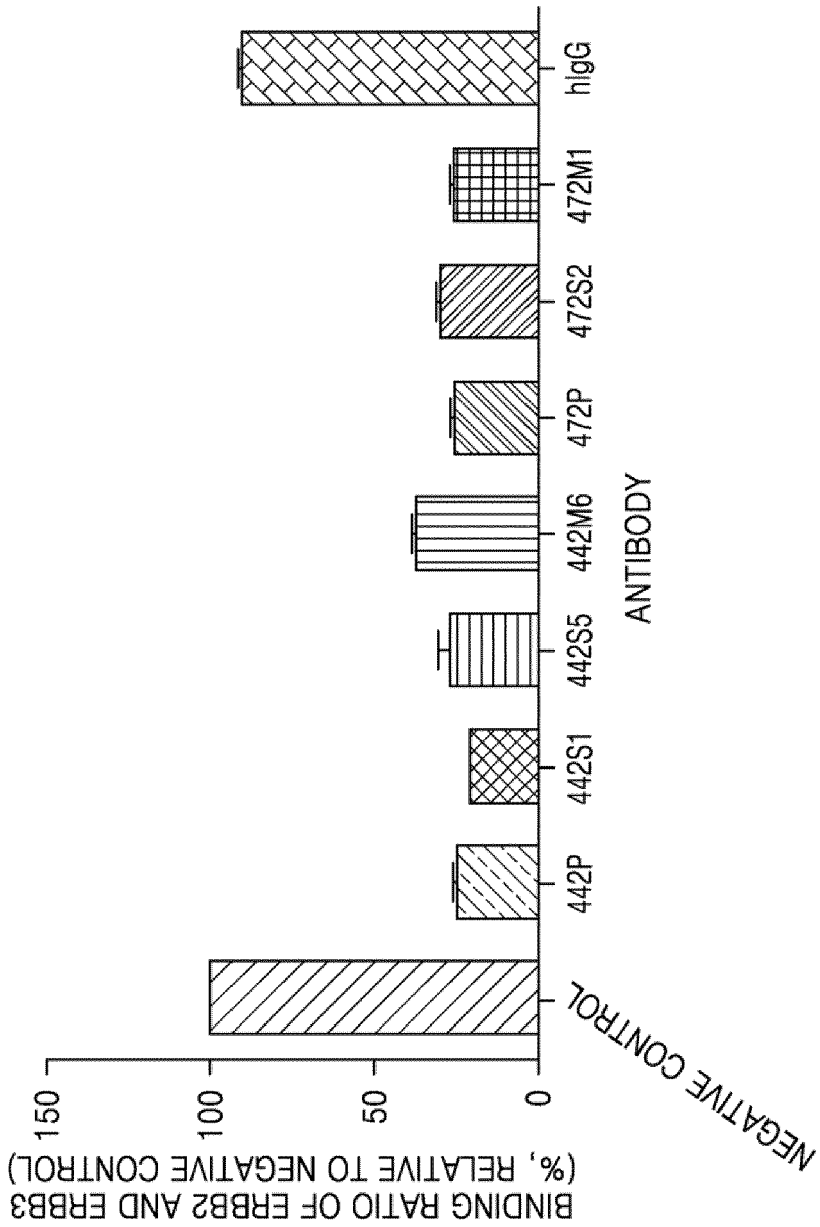
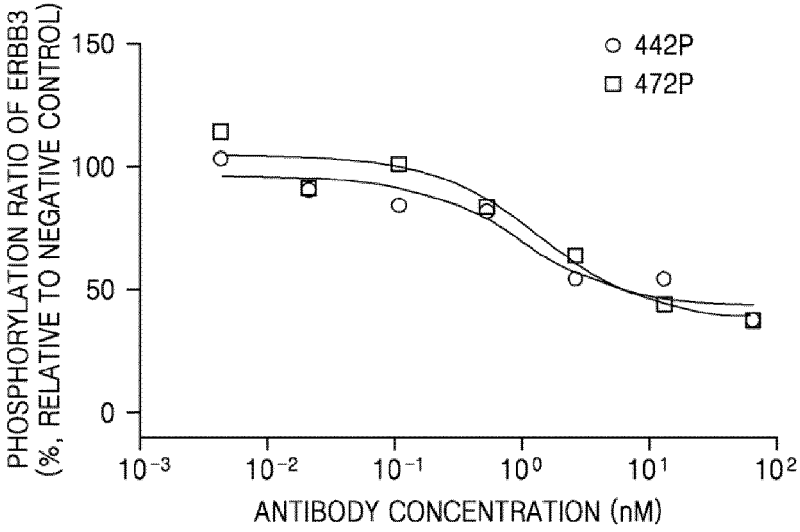

BINDING RATIO OF ERBB2 AND ERBB3
(%, RELATIVE TO NEGATIVE CONTROL)
150
100
50
0
NEGATIVE CONTROL
442P
442S1
442S5
442M6
472P
472S2
472M1
hIgG
ANTIBODY

Figure 4A


PHOSPHORYLATION RATIO OF ERBB3
(%, RELATIVE TO NEGATIVE CONTROL)
150
100
50
0
10⁻³
10⁻²
10⁻¹
10⁰
10¹
10²
ANTIBODY CONCENTRATION (nM)
442P
472P

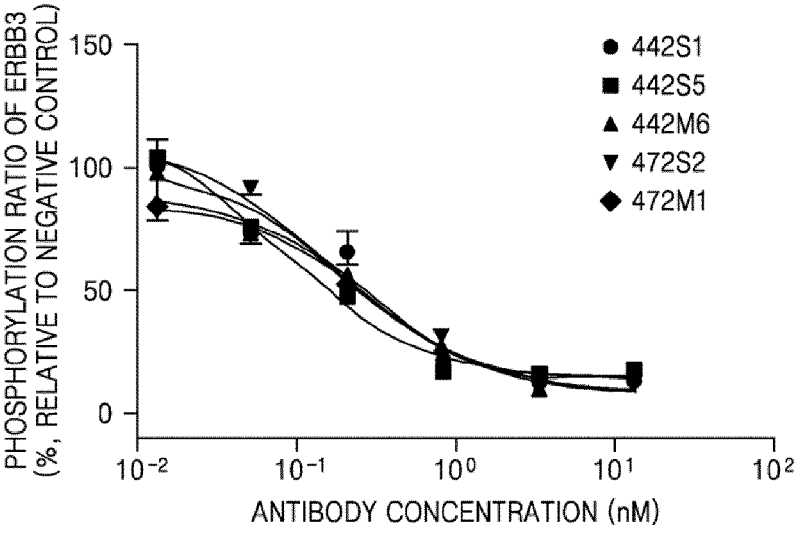

PHOSPHORYLATION RATIO OF ERBB3
(%, RELATIVE TO NEGATIVE CONTROL)
150
100
50
0
10⁻²
10⁻¹
10⁰
10¹
10²
ANTIBODY CONCENTRATION (nM)
442S1
442S5
442M6
472S2
472M1

Figure 4B

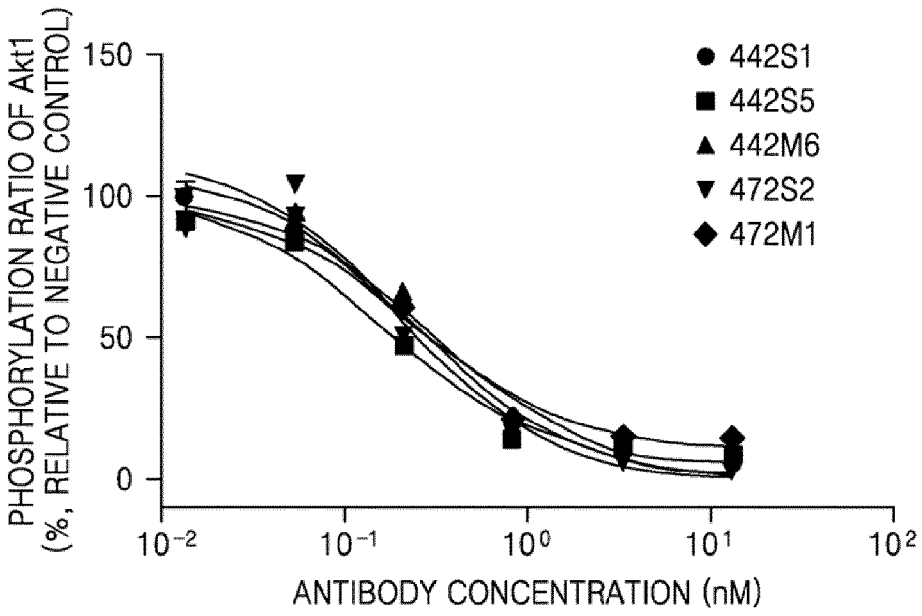

PHOSPHORYLATION RATIO OF Akt1
(%, RELATIVE TO NEGATIVE CONTROL)
150
100
50
0
10^{-2}
10^{-1}
10^{0}
10^{1}
10^{2}
ANTIBODY CONCENTRATION (nM)
442S1
442S5
442M6
472S2
472M1

Figure 5

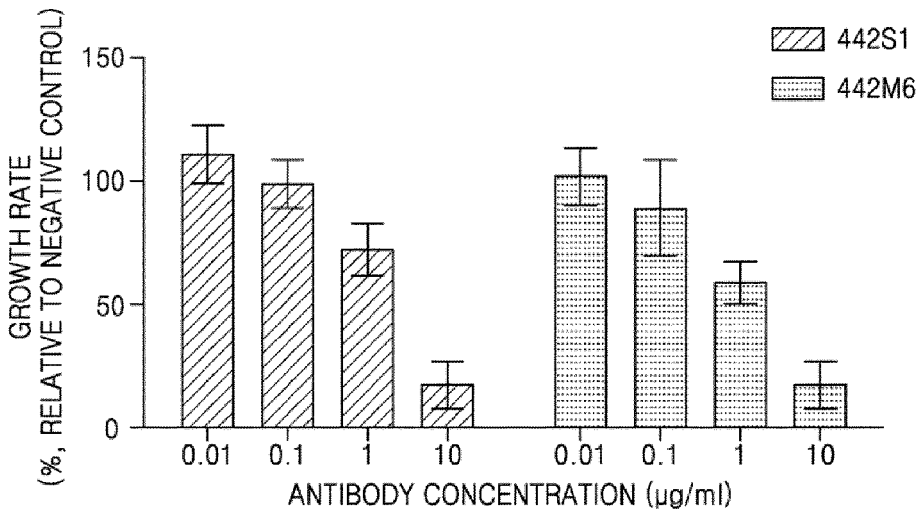

442S1
442M6
GROWTH RATE
(%, RELATIVE TO NEGATIVE CONTROL)
150
100
50
0
0.01
0.1
1
10
0.01
0.1
1
10
ANTIBODY CONCENTRATION (μg/ml)

Figure 6

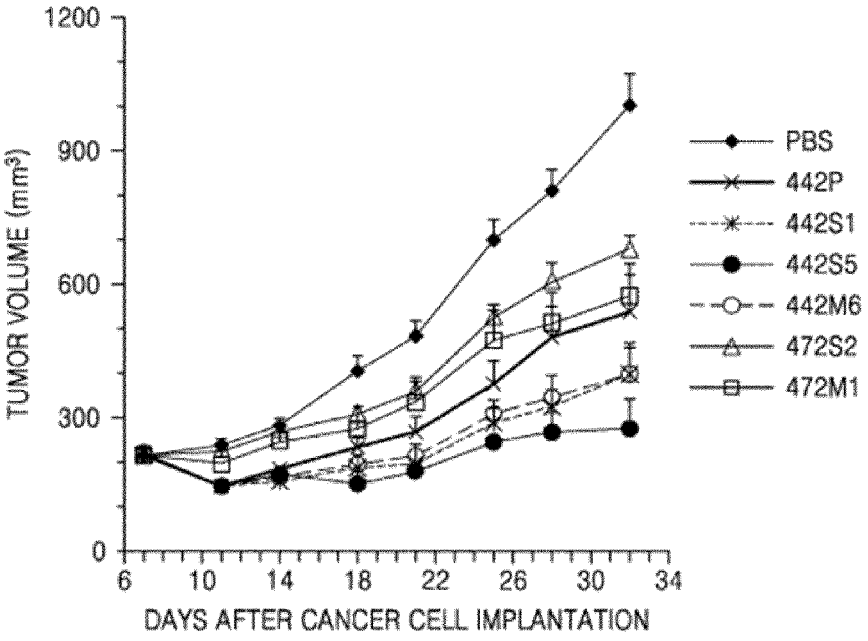

1200
900
600
300
0
TUMOR VOLUME (mm³)
6
10
14
18
22
26
30
34
DAYS AFTER CANCER CELL IMPLANTATION
PBS
442P
442S1
442S5
442M6
472S2
472M1

Figure 7

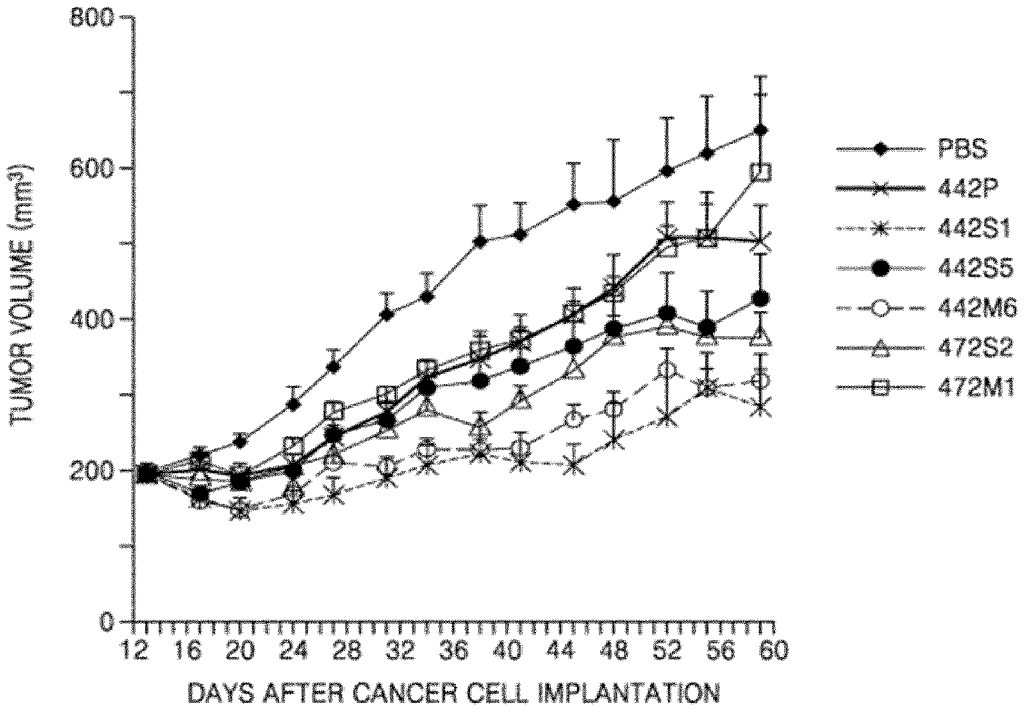

800
600
400
200
0
TUMOR VOLUME (mm³)
12 16 20 24 28 32 36 40 44 48 52 56 60
DAYS AFTER CANCER CELL IMPLANTATION
PBS
442P
442S1
442S5
442M6
472S2
472M1

Figure 8

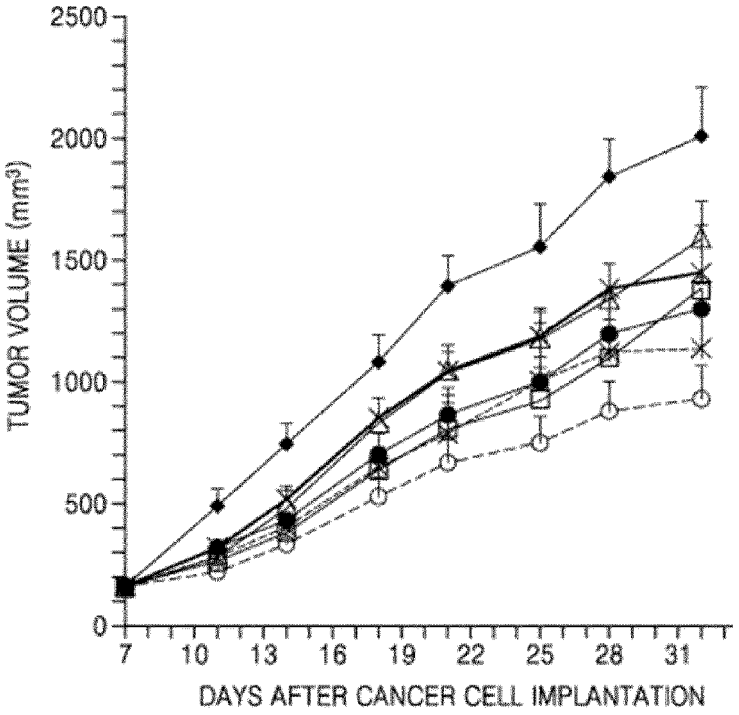

2500
2000
1500
1000
500
0
TUMOR VOLUME (mm³)
7
10
13
16
19
22
25
28
31
DAYS AFTER CANCER CELL IMPLANTATION

Figure 9

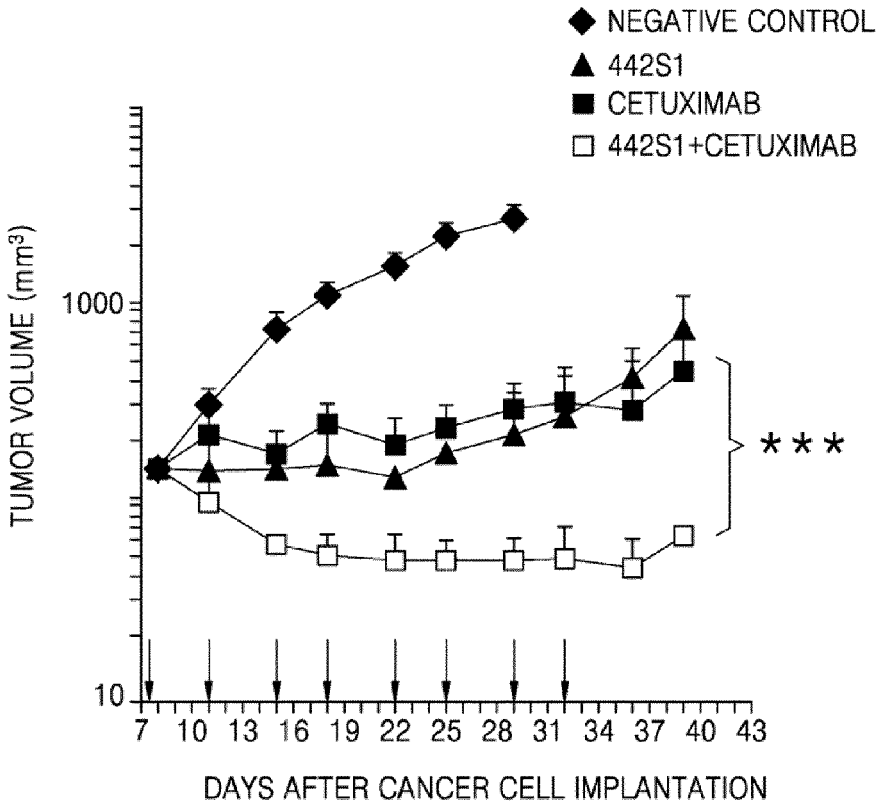

NEGATIVE CONTROL
442S1
CETUXIMAB
442S1+CETUXIMAB
TUMOR VOLUME (mm3)
1000
10
***
7 10 13 16 19 22 25 28 31 34 37 40 43
DAYS AFTER CANCER CELL IMPLANTATION

Figure 10

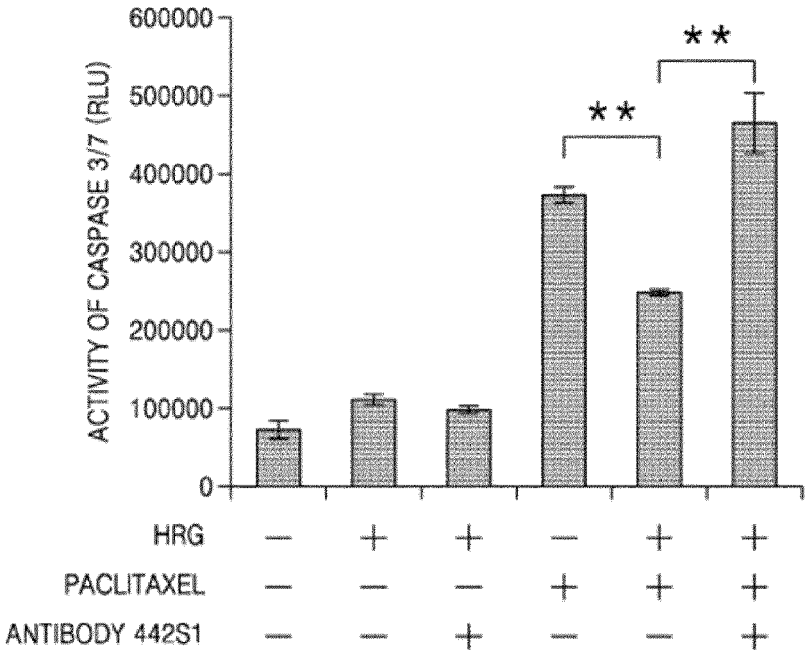

600000
500000
400000
300000
200000
100000
0
ACTIVITY OF CASPASE 3/7 (RLU)
**
**
HRG
PACLITAXEL
ANTIBODY 442S1

Figure 11

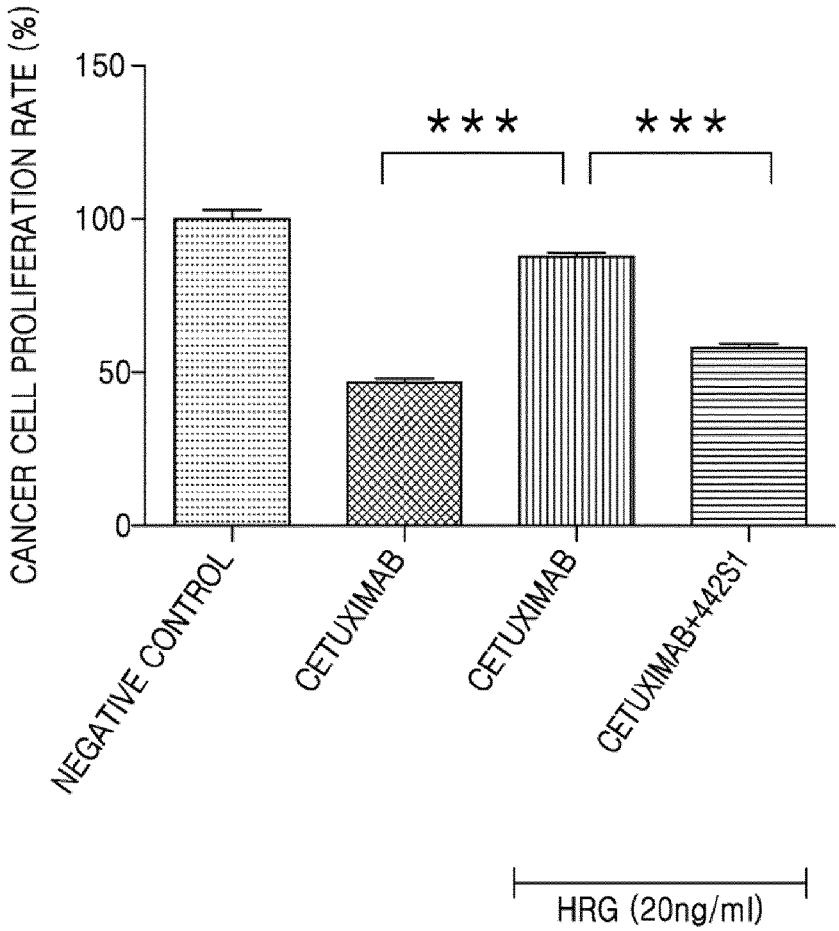
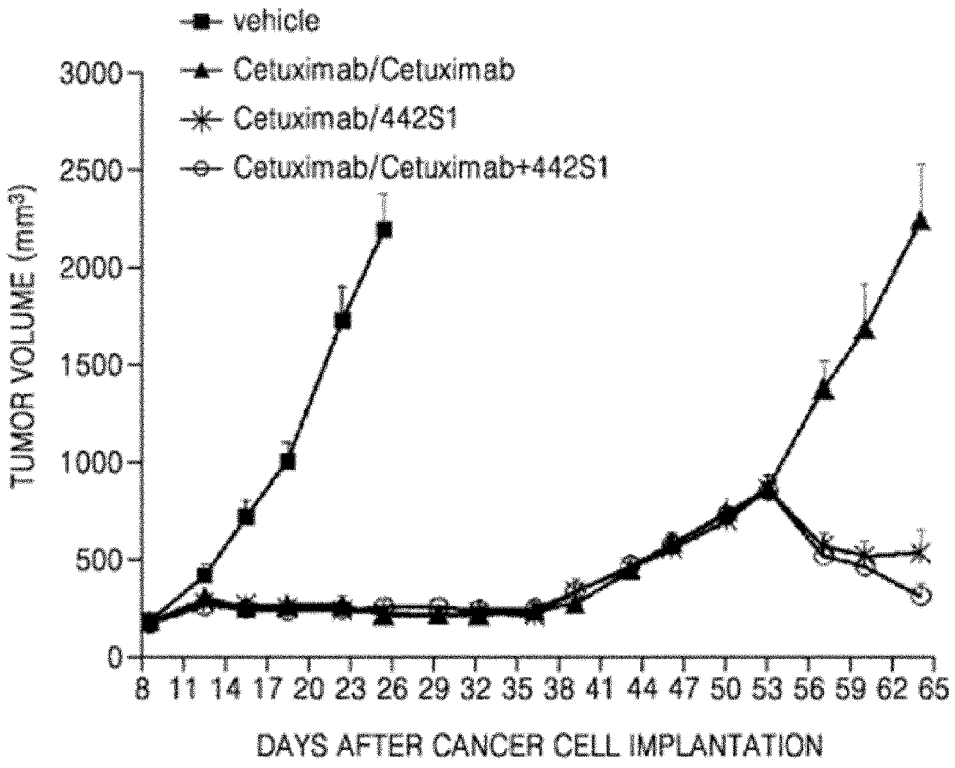

CANCER CELL PROLIFERATION RATE (%)
150
100
50
0
***
***
NEGATIVE CONTROL
CETUXIMAB
CETUXIMAB
CETUXIMAB+442S1
HRG (20ng/ml)

Figure 12


vehicle
Cetuximab/Cetuximab
Cetuximab/442S1
Cetuximab/Cetuximab+442S1
TUMOR VOLUME (mm³)
3000
2500
2000
1500
1000
500
0
8 11 14 17 20 23 26 29 32 35 38 41 44 47 50 53 56 59 62 65
DAYS AFTER CANCER CELL IMPLANTATION

Europäisches Patentamt
European Patent Office
Office européen des brevets

EUROPEAN SEARCH REPORT

Application Number
EP 20 19 6712

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	NADEGE GABORIT ET AL: "Emerging anti-cancer antibodies and combination therapies targeting HER3/ERBB3", HUMAN VACCINES AND IMMUNOTHERAPEUTICS, vol. 12, no. 3, 3 November 2015 (2015-11-03), pages 576-592, XP055405052, US ISSN: 2164-5515, DOI: 10.1080/21645515.2015.1102809 * whole document, especially section "Monoclonal Antibodies Targeting HER3" and Tables 1, 2 *	1-7	INV. C07K16/32 C07K16/28 A61K39/395 A61K31/00 A61P35/00
X	AURISICCHIO L ET AL: "The promise of anti-ErbB3 monoclonals as new cancer therapeutics", ONCOTARGET, IMPACT JOURNALS LLC, UNITED STATES, vol. 3, no. 8, 10 August 2012 (2012-08-10), pages 744-758, XP002690058, ISSN: 1949-2553, DOI: 10.18632/ONCOTARGET.550 * whole document, especially section "Monospecific anti-ErbB3 antibodies" and Table 1 *	1-7	TECHNICAL FIELDS SEARCHED (IPC) C07K A61K A61P
X	GIANLUCA SALA ET AL: "EV20, a Novel Anti-ErbB-3 Humanized Antibody, Promotes ErbB-3 Down-Regulation and Inhibits Tumor Growth In Vivo", TRANSLATIONAL ONCOLOGY, vol. 6, no. 6, 1 December 2013 (2013-12-01), pages 676-IN9, XP055168432, ISSN: 1936-5233, DOI: 10.1593/tlo.13475 * the whole document *	1-7	

-/--

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	18 December 2020	Luyten, Kattie

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

Europäisches Patentamt
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EUROPEAN SEARCH REPORT

Application Number
EP 20 19 6712

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	LI ZHANG ET AL: "ERBB3/HER2 Signaling Promotes Resistance to EGFR Blockade in Head and Neck and Colorectal Cancer Models", MOLECULAR CANCER THERAPEUTICS, vol. 13, no. 5, 5 May 2014 (2014-05-05), pages 1345-1355, XP055582372, US ISSN: 1535-7163, DOI: 10.1158/1535-7163.MCT-13-1033 * the whole document *	1-7	
X	US 2013/330772 A1 (VINCENT SYLVIE [US] ET AL) 12 December 2013 (2013-12-12) * whole document, especially the Examples, Tables and Figures 14, 22-24 *	1-7	
X	US 2013/084297 A1 (DALY CHRISTOPHER [US] ET AL) 4 April 2013 (2013-04-04) * whole document, especially the Examples and Tables *	1-7	
X	US 2012/328623 A1 (TAKAHASHI NOBUAKI [JP]) 27 December 2012 (2012-12-27) * whole document, especially the Examples and Figure 4 *	1-7	TECHNICAL FIELDS SEARCHED (IPC)
X	WO 2015/048008 A2 (MEDIMMUNE LLC [US]) 2 April 2015 (2015-04-02) * the Examples, especially Examples 5-6, and Figures 19-33 *	1-7	

-/--

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	18 December 2020	Luyten, Kattie

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L : document cited for other reasons

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EUROPEAN SEARCH REPORT

Application Number
EP 20 19 6712

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	SHUILIANG WANG ET AL: "Therapeutic targeting of erbB3 with MM-121/SAR256212 enhances antitumor activity of paclitaxel against erbB2-overexpressing breast cancer", BREAST CANCER RESEARCH, CURRENT MEDICINE GROUP LTD, GB, vol. 15, no. 5, 29 October 2013 (2013-10-29), page R101, XP021169114, ISSN: 1465-5411, DOI: 10.1186/BCR3563 * the whole document *	1-7	
X	EP 2 544 680 A2 (MERRIMACK PHARMACEUTICALS INC [US]) 16 January 2013 (2013-01-16) * the Examples and Figures *	1-7	
			TECHNICAL FIELDS SEARCHED (IPC)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	18 December 2020	Luyten, Kattie

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T : theory or principle underlying the invention
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